VOL. 93 ● NÚM. 1-12
ENERO - DICIEMBRE 2001

1902

ASOCIACIÓN MÉDICA DE PUERTO RICO

BOLETÍN

ASOCIACIÓN MÉDICA *de Puerto Rico*

ASOCIACIÓN MÉDICA DE PUERTO RICO

BOLETIN

VOL. 93 • NÚM. 1-6 • ENERO a JUNIO 2002

Catalogado en Cumulative Index e Index Medicus.
Listed in Cumulative Index and Index Medicus. No. ISSN - 0004-4849

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Publicación trimestral - $40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.
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Boletín de la Asociación Médica de Puerto Rico is published quarterly for $40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908-9387.
"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, San Juan, Puerto Rico 00908-9387.

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EDITORIAL

Dr. Pedro M. Mayol, FAAP, FCCP*
Dr. Robert Hunter Mellado, FACP**

Este número del Boletín tiene incluido artículos de interés general, experiencias clínicas y revisiones de literatura que servirán como trasfondo del manejo clínico de pacientes.

Compartir con ustedes una nueva edición de nuestro Boletín, fue una experiencia enriquecedora;
A petición del actual Presidente de la Asociación Médica de Puerto Rico, el Dr. Fernández Filiberti, tanto el Dr. Hunter y este servidor nos envolvimos en facilitar el que el Boletín se publicara una vez más.

El Dr. Robert Hunter Mellado, Co-Editor de este número una vez más fue el responsable de la evaluación y selección de los artículos, por lo cual reconocemos su valiosa y desinteresada colaboración.

Mientras se preparaba esta edición, y a la luz de la implementación de la Ley de la Colegiación de los Médicos, entiendo que el futuro está fértil para la evaluación de este tema y otros para una próxima edición del Boletín.

Nuestra recomendación a los futuros editores, es que consideren la publicación de temas vitales en la práctica de la Medicina Actual, tales como la Reforma de Salud y el tema de la Responsabilidad Profesional.

El tema de la responsabilidad profesional es un tema sensitivo y emocional, ya que requiere una evaluación ponderada y exhaustiva; es sumamente complejo y envuelve aspectos relacionados, por ejemplo; la tecnología, las estructuras de prestación de servicios, aspectos clínicos psicológicos, liderato, manejos administrativos, ambientes culturales y socioeconómicos.

El Boletín de la Asociación Médica puede convertirse en el foro para discutir a profundidad los nuevos retos que tenemos todos los profesionales relacionados con la prestación de servicios en este nuevo siglo....

Es esencial que el Boletín continúe publicándose; Confío que la Asociación Médica de Puerto Rico continuará en su esfuerzo de la publicación del mismo....

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MENSAJE

MENSAJE DEL PRESIDENTE
DR. RAFAEL FERNANDEZ FELIBERTI

Mi interés en la Asociación Médica de Puerto Rico comenzó desde mis años mozos, allá para el fin de la década de los cincuenta, cuando estaba en mi último año de la Escuela de Medicina de la Universidad de Puerto Rico. Fui Miembro Afiliado de esta honorable institución para la primera mitad de los sesenta (1962), cuando pasé gran parte de mi vida fuera de Puerto Rico haciendo mi internado, tres años de servicio en la Marina y mi residencia en la especialidad. Regresé a Puerto Rico en julio del 1966, pero ya desde enero de ese año pasé a ser Miembro Activo y lo he sido consecutivamente hasta el presente.

He tenido la oportunidad de participar activamente en nuestra querida sociedad como soldado de fila, siendo miembro de la Cámara de Delegados en un sinnúmero de ocasiones, siendo miembro de varios Comités y del Consejo de Política Pública hace un número de años. Como oficial he tenido la oportunidad de ser Presidente del Distrito Este, Vicepresidente de la Cámara de Delegados y Vicepresidente de la Asociación Médica de Puerto Rico.

Debe ser evidente mi lealtad, amor y compromiso con esta organización. Creo conocerla bien a fondo y comparto fielmente su misión y sus principios. Es por eso que me siento profundamente honrado en poder dirigirme a ustedes ahora como su Presidente a través de ésta, su Prensa Médica.

El 2002 es el año del Centenario de la Asociación Médica de Puerto Rico. Se ha programado un número de actividades a través de todo este año. Están incluidas, conferencias educativas, actividades de servicio al pueblo, funciones culturales y religiosas, una Cena-Gala para fin de año y unas actividades para el pueblo cuando se abrirán las puertas de nuestra sede para beneficio de todos nuestros amigos. Ya serán informados a través de todos los medios.

En este año tan importante para la historia de nuestra Asociación y de nuestro país, que bonito sería poder decir yo era miembro o me hice miembro de la Asociación Médica de Puerto Rico durante su Centenario. **Te exhorto a mantener tu membresía al día o a unirte a nosotros hoy**.

Artículos Especiales:

First Report of a Family with Lynch Syndrome Type II in Puerto Rico

Rafael A. Mosquera, M.D.*; Henry T. Lynch, M.D.**

Abstract

Colorectal cancer (CRC) incidence in Puerto Rico has increased prodigiously since incidence figures were first recorded in 1950. Implications for hereditary nonpolyposis colorectal cancer (HNPCC) in concert with this increased CRC incidence are discussed. A family with the Amsterdam-positive criteria of the Lynch syndrome II variant, identified in the eastern area of Puerto Rico, is described. As far as we can determine, this is the first such report of this disorder in Puerto Rico.

Introduction

Since 1950 the incidence of colorectal carcinoma (CRC) in Puerto Rico has increased in males from 5.4 to 28.2 per 100,000, and in females from 6.4 to 24.7 per 100,000 (crude and age adjusted) (1). This is a 5-fold increase in males and almost a 4-fold increase in females in the last 41 years. CRC is the second most common cancer in Puerto Rico for males and the third for females (1,2). In 1991, 7% of the 2,548 male cancer deaths and 8% of the 1,724 female cancer deaths were attributable to CRC.

The crude rates of CRC in Puerto Rico are consistently increasing both for males and females. At the beginning of the new millenium there will be approximately 1,103 new cases of CRC in Puerto Rico (1). The reason for such an increase in the incidence of CRC in Puerto Rico remains elusive. There are several possible explanations for this increase in CRC. Underreporting when its assessment began in the 1950s is one possibility. Dietary changes, as described in the Beuchamp study (3) in the decade from 1955 to 1965, must also be considered. There was an increased per capita income, from $431 to $900 which coincided with a change from an agricultural economy to an industrialized economy. This economic improvement changed dietary habits. Meat consumption increased 71%, from 69.4 lbs. per capita in 1955 to 119.3 lbs. per capita in 1965. There was also a reduction in the use of carbohydrates and fiber and an increase in the use of proteins from milk and eggs. The changes from an agricultural to an industrialized economy also caused a reduction in physical activity (because of new sedentary jobs at factories), which has emerged recently as a factor consistently associated with an increased risk of colon cancer. Genetics and/or its interaction with environmental agents may also partially explain this increase in CRC. Expectantly, about 5 to 10% (55-110 cases) of CRC per annum are likely to be attributed to a hereditary etiology.

Our purpose is to describe a family with hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as Lynch syndrome, which is believed to be the first such family with this disease reported in Puerto Rico. Recognition of HNPCC, which constitutes the most common genetic CRC variant, could provide a partial explanation for the increased incidence of CRC wherein environmental factors may mask an otherwise latent cancer-prone genotype. Documentation in additional families could provide a basis for improved cancer control through the implementation of highly targeted surveillance and management.

Case Report

The proband (patient V-I, Figure 1) is a 32-year-old male who presented

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This article was supported by revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the State of Nebraska or the Nebraska Department of Health and Human Services.
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at age 26 with gastroesophageal reflux and epigastric pain. Upper endoscopy revealed hyperemia of the distal esophagus. Dietary modifications and treatment with Prilosec 20mg p.o. were administered and his response to this treatment was excellent. Two months later, he was seen in the emergency room with a stabbing acute severe right lower quadrant colic-like pain, which had increased in frequency during a period of several weeks, culminating with obstipation during the three days preceding this visit. Physical examination showed peristaltic rushes. His abdomen was exceedingly tender with rebound and guarding. KUB films showed evidence of mechanical intestinal obstruction, confirmed by an abdominal CT scan, which showed a mass at the cecum which appeared to be causing the obstruction.

Exploratory laparotomy confirmed an obstructing lesion at the cecum and a right hemicolectomy with ileal transverse anastomosis was performed. Pathology findings showed a moderately differentiated adenocarcinoma with ulceration, perforation, and abscess formation, which involved the full thickness of the bowel wall and extended into the pericolonic fat. Twelve pericolonic lymph nodes were negative. Findings were consistent with a Dukes B-2 lesion of the cecum. 5FU-based chemotherapy with levamisole was then initiated. The patient was followed over a period of six years with annual colonoscopies. His only finding during this surveillance was a 4cm benign hemangioma in the right lobe of the liver. He was referred to the HNPCC Family Registry, where a pedigree (Figure 1) was constructed.

The family history revealed that his mother (IV-1) had manifested proximal colon cancer at age 35 years. Her record review disclosed morbid obesity and the presence of diarrhea for approximately five years without weight loss or rectal bleeding. Hypochromic microcytic anemia was attributed to menometrorrhagia, which was under evaluation by a gynecologist. Her stools were found to be positive for occult blood. Barium enema revealed a stenosing lesion at the proximal colon and a right hemicolectomy was performed.

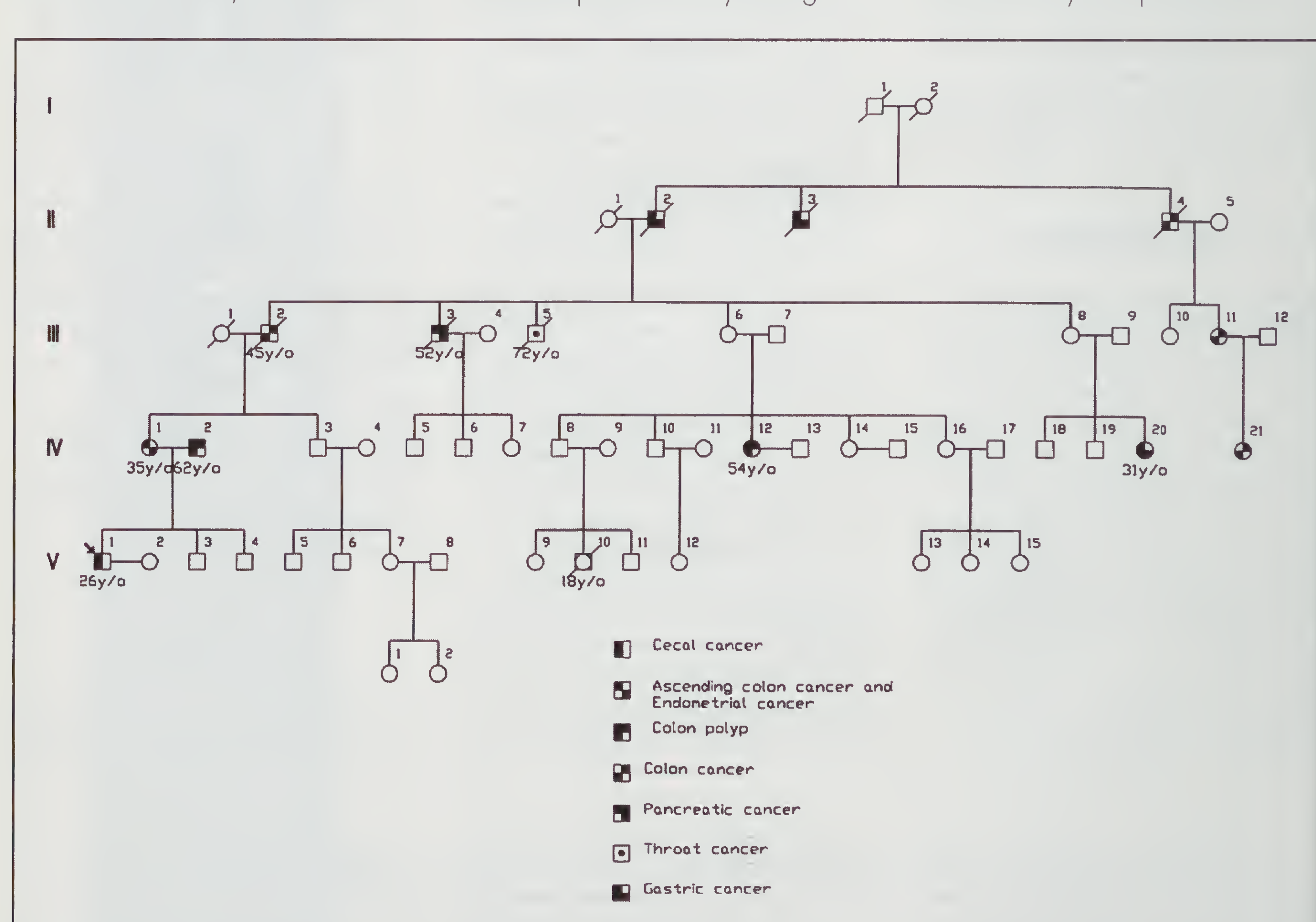


Figure 1. Pedigree of Puerto Rican family showing hereditary pattern consistent with HNPCC.

Pathology disclosed three mucin-producing adenocarcinomas, which appeared to originate from mixed villous adenomatous polyps, two of which were in the ascending colon near the ileocecal valve while the third was at the hepatic flexure. Six of 39 regional lymph nodes showed metastatic adenocarcinoma. She was staged as a Dukes C-2 adenocarcinoma and was treated with 5FU and Leucovorin. Fourteen months later, she presented with severe menometrorrhagia. Gynecologic consultation was requested and a dilatation and curettage revealed a papillary adenocarcinoma of the endometrium. She underwent radiation therapy and total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Her compliance for follow-up colonoscopy was poor, with only one performed over a period of eight years. She appeared to be in denial, was extremely anxious, and indicated that she was fearful about developing another malignancy. She was referred to the HNPCC registry at Ryder Memorial Hospital in Humacao, Puerto Rico, and underwent genetic counseling. She agreed to colonoscopy, which was negative.

A detailed family history showed that her father (III-2, the proband's maternal grandfather) was a 45-year-old male who had medical findings consistent with liver metastases secondary to a presumptive diagnosis of CRC. No further medical information was available on him. The proband's maternal great-grandfather (II-2) died at age 55 with a presumptive diagnosis of gastric carcinoma. This individual had two brothers (II-3, II-4) who manifested gastric and colon cancer respectively. The proband has two brothers; one is under follow-up with annual colonoscopy while the second is being contacted for colonoscopic surveillance and genetic counseling. Lymphoblastoid cell lines were analyzed for mutations in hMLH1 and hMSH2 at the laboratories of Bert Vogelstein, M.D., Johns Hopkins University. The findings were negative for these HNPCC germ-line mutations. The proband's family has been encouraged to undergo appropriate colonoscopic and gynecologic surveillance in accord with the surveillance and management strategies recommended for HNPCC (4,5).

Discussion

Classification of Lynch syndromes Lynch syndrome I (hereditary site-specific CRC) is characterized by CRC, often at a young age (mean age 44 years); predominance of proximal colon cancers (70% proximal to the splenic flexure); an increased frequency of synchronous and metachronous CRCs; an autosomal dominant mode of inheritance attributable to a germ-line mutation in one of the mismatch repair (MMR) genes, most commonly hMSH2 or hMLH1; accelerated CRC carcinogenesis; and frequent finding of distinguishing pathology features in CRC, particularly poorly differentiated tumors with an excess of mucoid findings and signet cells, peritumoral lymphocytic infiltration, and Crohn's-like reaction. Improved survival of CRC has been identified when compared by staging with sporadic CRC controls (6). Lynch syndrome II displays all of the aforementioned features of Lynch syndrome I but differs by virtue of an increased frequency of certain extracolonic cancers, namely, carcinoma of the endometrium, ovary, stomach, small bowel, hepatobiliary system, transitional cell carcinoma of the ureter and renal pelvis, and cancer of the breast and brain (7,8).

HNPCC results from a mutation in one of a series of MMR genes. These MMR genes have been referred to as hMSH2, hMLH1, hPMS2, hMSH3, hMSH5, and hMSH6. hMLH1 and hMSH2, the most common mutations, are believed to account for about 60-70% of HNPCC families harboring a known HNPCC germ-line mutation. Affected individuals inherit a mutation in one of these alleles and the second mutation is acquired in the wild-type allele. The target cell is then less able to repair DNA mismatch errors. Tumors composed of such cells characteristically manifest microsatellite instability (MSI) and are said to have replication error phenotype (RER+). Most of the tumors arising in HNPCC are RER+, while about 15% of apparently sporadic CRCs are RER+. Sporadic RER+ tumors have clinical pathologic features which are strikingly similar to those observed in HNPCC (8).

Molecular genetic findings have enabled hereditary CRC to be divided into two groups:
(a) tumors that show MSI positivity, occur more frequently in the right colon, have diploid DNA, harbor characteristic mutations such as transforming growth factor type II receptor and BAX, and behave indolently, of which HNPCC is an example; and (b) tumors with chromosomal instability (CIN), which tend to be left-sided, show aneuploid DNA, harbor characteristic mutations such as K-ras, APC, and p53, and behave aggressively, of which familial adenomatous polyposis (FAP) is an example (4).

To standardize the selection criteria for HNPCC and to promote collaboration, a group known as the International Collaborative Group on HNPCC (ICG-HNPCC) was formed. During its first meeting in Amsterdam, the Netherlands, a set of selection

criteria was developed (9), known as the Amsterdam Criteria (AC I), which focused exclusively on CRC. Because of its restrictive features, the Revised Amsterdam Criteria (AC II) were then devised to include extracolonic malignancies (10).

Accelerated CRC carcinogenesis Adenomas are usually the precursor lesions for CRC in HNPCC (11-14). In addition, the adenomas often show an accelerated course to malignancy (15). Specifically, a tiny colonic adenoma in Lynch syndrome may evolve to CRC in only 2 to 3 years in contrast to 8 to 10 years for the general population. Conse-quently, we recommend that patients with HNPCC have surveillance colonoscopy initiated at age 25 and that it be performed at least every other year, but preferably annually.

Cancer prevention

Järvinen et al. (16,5) have shown that colonic screening significantly decreased the incidence of CRC by 62% in healthy individuals from families with HNPCC. Malignant lesions are often identified at an early stage (Dukes A or B). When CRC is identified, subtotal colectomy should be done due to the significant increased lifetime risk for metachronous CRCs (17).

Patients with Lynch syndrome II need to be closely followed for the development of extracolonic primary cancers. We recommend annual endometrial ultrasound and/or vacuum curettage beginning at age 30. Women at high risk presenting with CRC should have the option of prophylactic total abdominal hysterectomy-bilateral salpingo-oophorectomy if their families have been completed (17,18). Education and genetic counseling should be initiated in the late teens (18).

First Puerto Rican HNPCC family

This is the first family identified and described with the Lynch syndrome II variant in Puerto Rico. Although families with these hereditary characteristics account for only 2-8% of all patients presenting with CRC (19), the hereditary component, once confirmed, in concert with knowledge of its natural history, will help such patients to improve their prognosis, and reduce their morbidity and mortality, through colonoscopic surveillance. The pedigrees (see Figure 1) of families such as this need to be developed in order to asses the hereditary characteristics and risk for CRC and extra-colonic cancer in the family members, so that the appropriate screening can be provided to high-risk patients (first-degree relatives of Lynch syndrome cancer affecteds). This Lynch syndrome II family formed the basis for a registry of similar HNPCC families in Puerto Rico. Twenty-eight HNPCC families are currently under investigation in this registry, forming an excellent resource for cancer prevention and research in Puerto Rico.

To decrease the incidence of CRC in Puerto Rico, the government, through the Health Department, should develop educational programs dealing with how Puerto Ricans can improve their dietary habits by including five servings of fruits and vegetables per day, and also dealing with how to decrease the sedentary lifestyles of the populace. This may then contribute to a decrease in CRC incidence. Moreover, it harbors the potential of decreasing the development of coronary heart disease, hypertension and diabetes.

However, the issue of dietary factors in CRC etiology and control is highly complex and controversial. Specifically, Alberts et al. (20) and Schatzkin et al. (21) tested the hypothesis as to whether dietary intervention can inhibit recurrent colorectal adenomas, the main precursors of carcinoma of the large bowel. These studies indicated that a low-fat, high-fiber diet does not protect against recurrent adenomas. These data seem to weaken the hypothesis that a high-fat, low-fiber diet in Puerto Rico may have contributed to the steady increase in the incidence of CRC.

Germ-line mutations in the hMLH1 or hMSH2 genes were not found in the family discussed in this paper. Currently, in only about 40–70% of apparent Lynch syndrome families will germ-line mutations be identified. Clearly mutations in other genes, including hPMS2, hMSH3 and hMSH6, may be present but were not investigated in this family. As discussed by Syngal (22), the inability to identify the germ-line mutations in families with characteristics of HNPCC does not exclude those families from the possibility of harboring HNPCC.

We have described a patient in this family with two metachronous primary carcinomas of the colon (the proband's mother; IV-1), who also developed endometrial carcinoma. The characteristic genetic transmission to her child (using AC II criteria) is particularly consonant with the Lynch syndrome II variant of HNPCC. This case report describes the first family to be found in Puerto Rico (Figure 1) with Lynch syndrome II. With this information, appropriate education and screening techniques have been recommended to this family. This observation has led to the development of an HNPCC registry, which was initiated in 1997. It is located at Ryder Memorial Hospital in Humacao, Puerto Rico. The Registry's goals are to identify families at increased cancer risk, develop their pedigrees,

and then orient family members at inordinately increased cancer risk to the available screening techniques. These patients will be referred to the gastroenterologist at their geographic practice area. If the patients qualify, blood samples will be obtained for investigation of germ-line mutations through the Hereditary Cancer Institute at Creighton University, Omaha, Nebraska. This process will help identify patients with an inordinately increased cancer risk and will have the potential to prevent the development of advanced lesions, improve survival, and decrease morbidity and mortality for high-risk patients.

Summary

This case report describes the first family with the Lynch syndrome type II in Puerto Rico. This observation has led to the development of a Hereditary Colorectal Cancer (HNPCC) Registry, which was initiated in 1997. It is located at Ryder Memorial Hospital in Humacao, Puerto Rico. The Registry's goal is to identify families at increased cancer risk, develop their pedigrees, provide genetic counseling, provide DNA testing in search of MMR mutations (in consenting patients), and orient family members at inordinately increased cancer risk to the available screening techniques. These patients will be referred to the gastroenterologist in that geographic practice area. If the patients qualify, blood samples will be obtained for investigation of germ-line mutations through the Hereditary Cancer Institute at Creighton University, Omaha, Nebraska. This process will help identify patients with an inordinately increased cancer risk and will have the potential to prevent the development of advanced lesions, improve survival and decrease morbidity and mortality for high-risk patients.

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Artículos Especiales:

Technetium-99m Sestamibi in the diagnosis of breast cancer

The Mayagüez Medical Center experience

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Summary

The most successful screening procedures for breast cancer are breast physical examination and mammography. However, mammography has a positive predictive value of 15-30% for nonpalpable malignancy and of 22% for palpable carcinoma; this results in a large number of biopsies on patients with benign lesions. Furthermore, the benefit of mammography in woman with dense breast tissue (<50 years old) has been questioned.

Different studies have shown that Scintimammography with Tc-99m has a high sensitivity and specificity for detecting breast cancer (average of 85% and 89%, respectively), with higher positive predictive value for palpable lesions (89%).

We reviewed retrospectively 35 records of patients that had Scintimammography in our institution, and the sensitivity, specificity, positive and negative predictive values were similar to other centers (100%, 76%, 62.5% and 100%, respectively). So, Scintimammography may be a complement for current diagnostic techniques for breast maligrancy in our setting.

Introduction

Carcinoma of the breast is the second most common carcinoma in American women and is the leading cause of death in women aged 35 to 54 (1).Currently, the most successful screening procedures for early carcinoma of the breast are breast physical examination and mammography (2,3). However, mammography has a positive predictive value of 15 to 30% for nonpalpable malignancy and a positive predictive value of only 22% for palpable carcinoma (2,3). The false negative rate is 10 to 15%, which corresponds to a sensitivity of only 80% (2,3). This results in a large number of biopsies on patients with benign lesions.

Fine needle aspiration and core needle biopsy are increasingly being used, but these have been associated with sampling errors. Excisional biopsy remains the "gold standard", but exposes patients to morbidity as well as the psychological and economic cost of a surgical procedure. A noninvasive, improved technique to select those who would most benefit from biopsy of the breast and reduce the number of negative biopsies is clearly of value.

Several groups have studied scintigraphic evaluation of a variety of malignancies. Technetium-99m Sestamibi (Tc-99m Sestamibi) is a cardiac perfusion agent that is approved for patients with coronary disease to identify damaged cardiac muscle. This agent has been used to identify brain tumors, parathyroid adenomas and thyroid carcinomas (1,4); several studies have evaluated the use of Tc-99m Sestamibi scintimammography in the detection of breast cancer, with reported sensitivity of 85% and specificity of 89%, and a positive and negative predictive value of 89% and 84% respectively (4).

The purpose of this study was to evaluate retrospectively the Tc-99m Sestamibi scintimammography experience in the detection of breast cancer in patients evaluated at the Mayaguez Medical Center.

Materials and Methods

The records of 35 female patients that had Tc-99 Sestamibi scan between February 1996 and October 2000 were reviewed. All patients had physical examination and mammographic evaluation; the study entry criteria consisted of a positive finding on mammography or

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a mass palpated on physical examination that required biopsy or fine needle aspiration cytology. Palpable masses had excisional biopsy or fine needle aspiration cytology, whereas nonpalpable abnormalities were diagnosed with excisional biopsy following guide wire placement. All patients gave written informed consent for scintimammography.

Scintimammography was performed in a dedicated nuclear medicine suite using a high-resolution collimator. The dose of Tc-99m Sestamibi for each patient was calculated according to patient's weight, administrating a single dose of 20 to 30 mCi intravenously in the contralateral arm of suspected breast lesion. Posterior oblique lateral images of each breast were collected for 10 minutes at 15 minutes post injection. This was performed with the patient prone and the breast in a dependent position. Anterior images were then collected with the patient's arms raised over her head.

The images were evaluated for abnormal uptake by a Nuclear Medicine physician (A.R) who was blinded to the patient's clinical evaluation and mammographic findings. A negative examination was defined as uptake equal to soft tissue uptake or bilateral diffuse mild uptake. A positive examination was defined as a region of focal uptake. Results of scintimammography were correlated with excisional biopsy in 34 lesions and with fine needle aspiration cytology in 1.

Results

Thirty-five records were reviewed. The mean age was 50.6 ± 11.9 (standard deviation). Thirty-four lesions were studied with biopsy and one with fine needle aspiration cytology; there were 18 palpable and 17 nonpalpable lesions in this series. Ten patients with positive results by scintimammography (SMM) were confirmed by biopsy or fine needle aspiration cytology (true positive results); seven of these lesions were palpable and 3 were nonpalpable. Nineteen lesions of the breast by SMM had true negative results; eight lesions were palpable and eleven were nonpalpable. Six had false positive findings and no patient had a false negative test based on the results of pathologic examination. False positive results included three palpable and three nonpalpable lesions. Five of these were fibrocystic disease and one was a fibroadenoma. The pathologic findings of biopsies and fine needle aspiration are listed in Table I.

Of the 17 suspicious nonpalpable lesions seen on mammography, 10 were fibrocystic disease (7 true negative and 3 false positive by SMM), 3 were ductal carcinoma (all true positives), 2 were cysts (true negatives), one was a fibroadenoma (true negative) and one was normal breast tissue (true negative).

In this study, scintimammography had an overall sensitivity of 100% and a specificity of 76%. The positive and negative predictive values were 62.5% and 100%, respectively, for detection of primary carcinoma of the breast.

Of note when comparing palpable to nonpalpable lesions (Table II) is the decrease in positive predictive value.

Discussion

Mammography is the recommended technique in the screening of breast cancer. The sensitivity of screening mammography with physical examination is between 85 and 90% (5), but 20 to 30% of breast malignancies occur in women younger than 50.The sensitivity of mammography in woman in this age group is often limited by dense breast tissue, and it has been questioned whether mammography is beneficial in this age group (6,7). Unfortunately, mammography has a poor positive predictive value of approximately 15 to 30% (5,8,9), resulting in most breast biopsies being performed for benign disease (10). Therefore, a need for a noninvasive and accurate imaging technique to further discriminate mammographically suspicious lesions requiring biopsy is clearly evident.

Table I.

Result of Tc-99m Sestamibi Scintimammography in 35 patients with pathologic correlation

Scintimammography	No. of lesions	Pathologic findings
True positive	10	10 infiltrating duct cell carcinomas
False positive	6	5 fibrocystic disease 1 fibroadenoma
True negative	19	12 fibrocystic disease 3 fibroadenomas 2 cysts 2 normal breast tissue
False negative	0	

Table II.

Overall and subgroup results of Scintimammography at Mayaguez Medical Center

	Overall(%)	Palpable(%)	Non-palpable(%)
Sensitivity	100	100	100
Specificity	76	72.7	78.5
Positive Predictive Value	62.5	70	50
Negative Predictive Value	100	100	100

Tc-99m Sestamibi (Miraluma TM) manufactured by the DuPont Merck Pharmaceutical Company, is a Federal Drug Administration approved radiopharmaceutical used mainly in patients with coronary disease to identify damaged cardiac muscle. Intravenous injection results in high concentrations of the tracer in the gallbladder and liver. The predominant target organ is the colon, which receives 3 rad after a 20 mCi injection. Several groups have demonstrated the preferential uptake of Sestamibi by in-vitro tumor cell lines (11,12). Data indicate that the majority of the tracer is taken up by mitochondria (13).

Our data indicate that scintimammography has a high sensitivity and specificity for detecting breast cancer. We have a sensitivity of 100%, with an average of 85% reported in other studies (4), and no difference between palpable and nonpalpable lesions. The specificity was lower (76%) when compared with the average of 89% reported in other studies (4), but criteria of interpretation for a positive lesion for breast cancer had not been well defined in initial reports, and since then, more specific criteria were described.

The evaluation of subgroups (palpable vs nonpalpable) doesn't affect the sensitivity in our study, but the positive predictive value is higher for palpable lesions (70% for palpable vs 50% for nonpalpable). Although the positive predictive value of our study is lower than the average of 89% reported in other studies (4), it is higher than the positive predictive value of mammography (15 to 30% for nonpalpable and 22% for palpable carcinomas) (3).

There is no abnormality in the uptake of Sestamibi associated to the presence of "dense" breasts in our study.

Resumen

Los procedimientos mas efectivos para la detección oportuna de cáncer de mama son el examen físico y la mamografía. Sin embargo, la mamografía tiene un valor predictivo positivo de solo 15 a 30% para lesiones no palpables y de 22% para las palpables, lo cual significa que un gran número de biopsias de seno se realizan a pacientes con lesiones benignas.

Diferentes estudios han demostrado que la Scintimamografia con Tc-99m tiene una alta sensibilidad y especificidad para el cancer de mama (un promedio de 85% y 89% respectivamente), con un valor predictivo positivo mayor para lesiones palpables (89%).

En este estudio se revisaron 35 expedientes de pacientes a los que se les realizó un Scintimamograma en nuestro Hospital, y se demostró que la sensibilidad, especificidad y los valores predictivos positivo y negativo eran similares a los de otros centros, por lo que consideramos que la Scintimamografía puede ser un complemento para los estudios diagnósticos de cancer de seno que utilizamos en nuestro medio.

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Artículos Especiales:

Prevalence and correlates of DSM-IV substance use disorders in Puerto Rico

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Abstract

We report the basic findings of a survey aimed at estimating rates of substance disorders in a probability sample of 4,709 household residents aged 15 to 64 years old. Lifetime use of alcohol was reported by 77.2%, and 10.7% reported ever using illicit drugs.
Overall, 14.7% of the sample met criteria for a lifetime substance disorder, and 4.9% for a past year disorder. The rates of lifetime disorders were 13.1% for alcohol and 4.1% for illicit drug. Past year abuse/dependence was 4.3% for alcohol and 1.3% for illicit drugs. Alcohol use disorders were associated with male gender, higher family annual income, being employed, and being married. Illicit drug use disorders were associated with male gender and younger age. Only 13.0% of respondents with a past year disorder reported using services for their disorder. A program of conti-nuous monitoring of substance using disorders is critical to establishing and monitoring effective policies.

Key Words:
Substance-related disorders, Puerto Rico, Community studies

Introduction

Substance use disorders have been recognized as a major public health problem worldwide. In countries where estimates are available, substance use disorders have been shown to be among the most prevalent of all mental disorders (1). In addition, excess rates of morbidity and mortality have been found among individuals with substance use disorders (2,3). Injection with illicit drugs has been reported in 129 countries and in 103 of these countries, the Human Immunodeficiency Virus has been detected among injection drug users (4). Surveillance data from the U.S. shows that the majority of new cases of infection with the Human Immunodeficiency Virus and the Hepatitis C Virus occur among substance abusers, their sexual partners and their offspring (5,6). Moreover, emerging epidemics of illicit drug abuse have been detected in many developing countries, most notably in Latin America (7).

Policies and programs aimed at stemming the rise of substance use disorders require systematic, ongoing, population-based epidemiologic surveillance systems to detect at-risk populations and monitor trends over time (8,9). However, until recently community surveys of substance use disorders were limited by the lack of adequate instrumentation with which to measure disorders in the general population and conduct cross-cultural comparisons. The diagnostic classification systems of substance use disorders have now converged to the point at which the criteria of the American Psychiatric Association (10) and that of the World Health Organization (11) are nearly identical (12). Concurrent with the increasing convergence of the diagnostic systems, a number of standardized diagnostic instruments that can be used in epidemiological studies of substance use disorders have been developed (1,13). Nonetheless, studies of substance use disorders in the general population continue to be limited to a small number of countries and are seldom repeated periodically.

In Puerto Rico, the only available estimates of substance use disorders date from the 1980s. Alcohol abuse was studied in 1984 with a probability sample of 1,554 adults 17 to 64 years old. In 1987, a

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Sources of Support: This study was conducted with funds from the Center for Substance Abuse Treatment under contract 270-95-0026.

follow-up study of 912 respondents from the 1984 sample provided an opportunity to examine illicit drug use disorders. Using a translated and adapted version of the Diagnostic Interview Schedule (14), these studies found lifetime alcohol abuse and/or dependence in 12.6% of the study sample; twelve-month prevalence was 4.8% (15). The lifetime prevalence of illicit drug use was found to be 8.0% and abuse/dependence 1.2% (16). These studies contributed the first estimates of the prevalence of substance use disorders in the population of Puerto Rico. Nonetheless, there were a number of limitations to these studies. They evaluated disorders with diagnostic criteria now superseded by the DSM-IV, and lacked adequate sample sizes with which to examine the covariates of illicit drug use disorders. Moreover, these estimates are now more than ten years old and are of limited use to policy makers, public health professionals, and researchers.

This article presents updated estimates of the rates of substance use disorders for the population of Puerto Rico. The study was designed to improve on the limitations of the previous studies in several ways. The study utilized a probability sample of 4,709 late adolescents and adults, over sampled high-risk areas and high-risk sub-populations to increase the probability of selecting drug abusers in the sample and implemented DSM-IV diagnostic criteria. The study design combined an area probability sample and telephone interviewing to ensure full coverage of the population while increasing the anonymity of the interview process. In this article we examine the rates of lifetime and past year abuse and dependence to alcohol and illicit drugs. We also assess the co-occurrence of substance use disorders with other psychiatric disorders and the use of formal services for treating substance use disorders.

Methods

Sampling and Subjects

The study sample was a multi-stage stratified cluster sample of all households in Puerto Rico. The target population from which the sample was drawn comprised all persons aged 15 through 64 years living in a household in Puerto Rico, including household members temporarily away. Excluded from the sample were homeless persons and those living in institutions. To increase the probability of selecting drug abusers in the sample, household segments in high-risk areas and young male adults were over sampled. The island territory was stratified on the basis of substance abuse problem indicators (i.e., per capita rates of drug overdose deaths, drug treatment admissions, drug violation arrests, and AIDS and Hepatitis B cases among drug users). Cluster analysis was used to derive a three-cluster solution corresponding to Municipalities with high, medium, and low rates of drug problem indicators. Household segments within each stratum were selected in three stages. In the first stage, a systematic selection of Census Block Groups (CBG) was made with probability proportional to the number of households in the CBG. The second selection stage consisted of a random selection of one block within each selected CBG. In the third stage, a segment of approximately 20 households was selected within each block. Four replicate samples of household segments were generated with identical procedures. A total of 468 household segments were selected, 266 in the high-risk stratum, 117 in the medium risk stratum, and 85 in the low risk stratum.

Fieldwork was conducted between January 1997 and March 1998. Field enumerators visited the selected household segments and listed all residents 18 to 64 years old. Adolescents 15 to 17 years old were enumerated in sample replicates three and four. The lists of residents were read over the phone and processed by a random selection software designed to select five males 18 to 34 years old, three females 18 to 34 years old, and one male and one female 35 to 64 years old from each household segment. In replicate samples three and four all the enumerated adolescents were selected for study participation.

Upon selection of respondents, field enumerators proceeded to contact respondents and invite them to participate. Participation was voluntary and anonymous. No identifying information was collected. Active and passive refusal conversion was attempted up to five times. Upon completing the interview, respondents were compensated with $20 for their time and effort. A field supervisor verified 10% of all enumerations.

Enumerators were able to visit 442 (94.4%) of the 468 selected household segments and to list the residents in 95.8% of the households. Of the selected individuals, 90.8% completed the assessment interview. These data yield an overall response rate of 85.8%.

Interviewing and Measures

The interview protocol consisted of a computer aided telephone interview. Consenting respondents were asked to dial the project telephone number and proceed to be interviewed. Respondents were also offered the use of a cellular phone to be interviewed. Telephone interviewing was intended to provide greater privacy and

anonymity to encourage truthful reports of drug use disorder symptoms.

Interviewers were trained during a 10-day period in the administration of the interview protocol and the use of the computerized interview. The computer program implemented question skip patterns, did not permit answers to be recorded outside of the valid ranges, and performed consistency checks. An interviewing supervisor was present at all times. The supervisor handled a console that allowed him or her to listen to the interviews. The supervision protocol entailed listening to five-minute stretches of all interviews and providing feedback to the interviewer at the end of the interview. On average, interviews lasted 25 minutes.

Drug use questions were designed so the respondent would not have to mention drug names aloud. Respondents were asked if they had used alcohol at least 12 times and each of eight classes of drugs at least five times for non-medical purposes. In addition to alcohol use, questions ascertained use of the following classes of drugs: amphetamines, cannabis (marihuana), cocaine, hallucinogens, inhalants, uploads, phencyclidine, sedatives, hypnotics, and anxiolytics. Affirmative responses were followed by questions ascertaining the period of most recent use. Respondents reporting not using alcohol at least 12 times or each of the other drugs at least five times were asked if they had ever used the substance.

Substance use disorders were measured with the World Health Organization Composite International Diagnostic Interview (CIDI, version 2.1) (17). This version of the CIDI implements the DSM-IV Psychiatric nosology (10) and ascertains the symptoms caused by alcohol and each of the nine classes of drugs and the age at which symptoms first and last occurred. The Spanish version of this instrument has been shown to be highly reliable (18). Respondents reporting use of each drug class at least once were asked the symptom questions. Computerized diagnostic algorithms examined the symptoms reported by each respondent and determined the presence or absence of dependence or abuse for each class of substance and the age of onset and the age of most recent occurrence of each disorder. Diagnosis of abuse and dependence were developed separately for each substance.

A screening instrument (UM CIDI Short Form 12 MONTH), was used to evaluate the probability of a respondent having a mood or anxiety disorder during the last 12 months. The UM CIDI Short Form was developed and validated by Kessler and Mroczek (19,20) as a screening scale of psychiatric disorder and nonspecific distress. The scale includes selected items from the full version of the University of Michigan CIDI derived empirically based on data obtained from the National Comorbidity Survey (21). Psychometric work on the specificity and sensitivity of the scales has been done in U.S. and Canadian populations (19,20,22). The mood disorders screened included major depression and dysthimia. The anxiety disorders screened included general anxiety disorder, phobias (specific, social, and agoraphobia), and panic attacks.

A series of questions ascertained the use of health services for problems related to alcohol or drugs during the 12 months previous to the interview. Respondents were asked if they had received services for their alcohol or drug problems from: physicians in private practice, primary care centers, general hospitals, or emergency rooms (general health sector); private psychiatrists, psychologists, counselors, alcohol/drug treatment programs, or in psychiatric hospitals (specialty sector). Respondents were also asked if they had attended self-help meetings such as meetings of Alcoholic Anonymous or Narcotic Anonymous.

Validity of Drug Use Self-Reports

As part of this study, hair specimens were collected from a sub-sample of respondents and tested for the presence of cocaine and heroin. Hair specimens were collected from respondents selected as part of the larger study and from a group of hard-core drug users living in households. The results of comparing self-reports with the toxicological tests have been analyzed elsewhere (23,24).
In summary, we found that light drug users were unlikely to disclose their drug use in the study interview.
The correspondence of the drug use reports with the toxicological results among the hard-core drug users, on the contrary, was high. Of special importance to the validity of the drug use disorder diagnoses was the finding that the drug use reports of respondents reporting disorder symptoms were more likely to be confirmed by the hair tests than those of respondents without disorder symptoms. These results suggest that drug use was under-reported in this study among respondents with a low risk of substance use disorders, and that the self-reports of respondents at risk of substance use disorders were reasonably accurate.

Statistical Analyses

Sample weights were calculated as the inverse of the probability of selection. Even though the response rates were generally above 90%, the proportion of household

Table I.

Comparison of sample gender and age distribution with 1995 U.S. Census population estimates for Puerto Rico

	Survey Sample		Population Estimates
Gender and Age Groups	unweighted n	weighted %	%
Males			
15 to 24 years old	1,243	13.6	14.0
25 to 34 years old	1,085	10.8	10.8
35 to 44 years old	189	9.9	9.5
45 to 54 years old	113	6.3	8.0
55 to 64 years old	76	3.9	5.6
Females			
15 to 24 years old	903	14.8	13.7
25 to 34 years old	677	11.3	11.8
35 to 44 years old	167	11.0	10.9
45 to 54 years old	142	10.9	9.3
55 to 64 years old	111	7.5	6.6

segments that could be accessed for enumeration decreased as the socio-economic index score of the segment increased. Post-stratification weighting was used to adjust for this pattern of non-response. Table I shows the unweighted and weighted gender and age distribution of the sample and compares the sample distribution with the gender and age distribution derived from the U.S. Census population estimates for 1995.

Weighted percents, design-adjusted standard errors, and chi square statistics were calculated using SUDAAN 7.5 (Research Triangle Institute, Research Triangle Park, NC, 1998) to take into account the stratification and clustering of the data.

Table II.

Prevalence of lifetime and past year alcohol and illicit drug use and DSM-IV abuse or dependence, Puerto Rico household population 15-64 years, 1997-1998 (n = 4,709)

	All Substances		Alcohol		Illicit Drugs	
	weighted %	SE	weighted %	SE	weighted %	SE
Lifetime						
Use	78.0	1.3	77.2	1.2	10.7	0.8
Abuse only	9.4	0.7	8.8	0.7	2.4	0.4
Dependence	5.3	0.7	4.3	0.6	1.9	0.3
Abuse and /or dependence	14.7	0.9	13.1	0.9	4.3	0.5
Past Year						
Use	31.1	1.0	30.5	1.1	2.6	0.4
Abuse only	3.4	0.3	3.1	0.3	0.8	0.2
Dependence	1.5	0.2	1.0	0.2	0.5	0.1
Abuse and /or dependence	4.9	0.4	4.1	0.4	1.3	0.2

Results

Estimates of lifetime and past year use, and DSM-IV substance use disorders are presented in Table II. Any lifetime use of alcohol was reported by 77.2% of respondents; close to a third reported use of alcohol during the past year. Any lifetime use of Illicit drugs was reported by 10.7% of respondents; 2.6% reported use of illicit drugs during the past year. Overall, 14.7% of the sample met criteria for a lifetime substance use disorder, and 4.9% for a past year substance use disorder. Respondents were nearly three times more likely to meet criteria for an alcohol use disorder than for a drug use disorder. Thirteen percent of the sample met DSM-IV criteria for lifetime alcohol abuse or dependence; 4.1% for lifetime abuse or dependence to illicit drugs. Past year estimates of abuse or dependence were 4.3% for alcohol and 1.3% for illicit drugs.

Lifetime rates of alcohol and illicit drug use disorders disaggregated by sociodemographic variables are shown in Table III. Males, respondents with higher family annual incomes, those employed or attending school and those married were significantly more likely to meet criteria for a lifetime alcohol use disorder. Illicit drug use disorders were significantly associated with male gender and younger age.

Estimates of associations between substance use disorders and mood and anxiety disorders are presented in Table IV. Respondents with a probable past year mood or anxiety disorder were twice as likely to have an alcohol use disorder than respondents without a mood or anxiety disorder. Respondents with a probable past year mood disorder were four times more likely to have a drug use disorder than respondents without a mood disorder and

Table III

Sociodemographic correlates of lifetime DSM-IV alcohol and illicit drug abuse or dependence, Puerto Rico household population 15-64 years, 1997-1998 (n = 4,709)

	Alcohol weighted %	p	Illicit Drugs weighted %	p
Gender				
male	21.0		6.5	
female	6.9	<0.01	2.5	<0.01
Age				
15-24 years old	11.4		4.9	
25-34 years old	14.4		5.6	
35-44 years old	14.8	0.10	5.0	<0.01
45-54 years old	15.9		3.4	
55-64 years old	8.0		0.2	
Race				
white	13.5		4.3	
black or mixed	12.3	0.53	4.2	0.87
Education				
< high school education	10.7		4.7	
high school education	12.7		3.3	
some college	15.4	0.11	4.7	0.40
college degree or more	16.0		4.2	
Urban/rural residence				
urban	14.0		4.7	
rural	10.7	0.11	3.2	0.18
Annual family income				
< $10,000	10.2		3.9	
$10,000 - $20,000	14.4		4.8	
$20,000 - $30,000	15.3	0.02	3.9	0.71
$30,000 - $40,000	22.0		8.5	
> $40,000	20.0		3.3	
Employment/student status				
not employed and not in school	10.3		4.1	
employed or in school	14.5	0.04	4.4	0.79
Marital status				
not married	11.0		4.1	
married or living as married	15.1	0.01	4.4	0.78

respondents with an anxiety disorder were nearly three times more likely to have a drug use disorder than respondents without an anxiety disorder. Alcohol and drug use disorders were also significantly associated to each other. Respondents with a disorder associated to one type of substance (alcohol or illicit drugs) were 13 times more likely to have met criteria for a disorder associated to the other type of substance.

The proportions of respondents with a past year alcohol or drug use disorder that utilized health services for their alcohol or drug use problems are shown in Table V. The table shows the use of services by the type of health care sector where services were received. Overall, only 13.0% of respondents with a past year substance use disorder reported using health services for their alcohol or drug problem. Respondents with an alcohol use disorder were less likely to use any service than respondents with a drug use disorder (11.9% vs. 23.9%). Respondents with an alcohol use disorder were more likely to use services in the general sector than in the specialized sector (9.5% vs. 5.0%). The reverse was true of respondents with a drug use disorder; 17.5% used services in the specialty sector and 10.6% in the general sector. Respondents with a drug use disorder were also more likely to attend meetings of self-help groups than respondents with an alcohol use disorder (5.6% vs. 1.6%).

Discussion

The results of this study show that substance use disorders are not uncommon in the population of Puerto Rico. We found that four percent of the population 15 to 64 years old had, at some point in their life, been affected by a disorder associated to the use of illicit drugs. By comparison, almost three times as many (13.1%) had developed a disorder associated to the use of alcohol. Further, the study estimated that close to five percent of the population 15 to 64 years old had a current substance use disorder (past year). In population terms, this prevalence means approximately 117,000 individuals; 35,000 of whom met criteria for substance dependence. Our study did not include homeless persons or institutionalized individuals. Although these populations are likely to have higher prevalence rates of substance use disorders, their size is small compared to the size of the household population.

Table IV

Associations between past year mood and anxiety disorders and past year alcohol and illicit drug abuse or dependence, Puerto Rico household population 15-64 years, 1997-1998 (n = 4,709)

	Past Year Alcohol Abuse/Dependence			Past Year Illicit Drug Abuse/Dependence		
Past Year Disorders	weighted %	OR	95%CI	weighted %	OR	95%CI
Mood disorder						
probable non case	3.7			1.0		
probable case	7.5	2.1	1.3 - 3.5	3.9	4.2	2.3 - 7.5
Anxiety disorder						
probable non case	3.7			1.0		
probable case	6.6	1.9	1.2 - 2.9	2.7	2.7	1.6 - 4.8
Alcohol abuse/dependence						
diagnostic negative	-			0.9		
diagnostic positive	-			10.4	13.2	7.3 - 24.1
Illicit drug abuse/disorder				-		
diagnostic negative	3.7			-		
diagnostic positive	33.5	13.2	7.3- 24.1			

Epidemiological catchment area analyses have found that estimates of the prevalence of substance use disorders increase only slightly when appropriately weighted data from homeless and institutionalized populations are joined to household data (25).

The lifetime prevalence of alcohol abuse or dependence in our study (13.1%) is very similar to the rate estimated in Puerto Rico in 1984 (12.6%) (15). Our estimate of lifetime illicit drug abuse or dependence (4.3%), however, is considerably higher than the previous estimate derived from the 1987 study of the household population in Puerto Rico (1.2%) (16). The difference between the illicit drug abuse estimate of 1987 and the current estimate can be due to differences in the methods of the two studies as well as to true increases in the prevalence of illicit drug abuse in Puerto Rico.

The 1987 study was a follow-up study of respondents surveyed in 1984. To be able to conduct follow-up interviews, researchers need to collect considerable personal information to make possible the relocation of respondents, thus decreasing the anonymity of the interview encounter. In our study, respondents were not asked any personal identifying information and the interview was conducted over the telephone. Even though a staff member had visited and recruited the respondent at home, the field personnel were unaware of the responses reported over the phone and the interviewer conducting the telephone interview did not know the respondents identity. Measurement instrumentation also differed between the two studies. The 1987 study implemented DSM-III-R nosology and our study instrument was based on the DSM-IV nosology. Tests of the differences between DSM-III and DSM-IV based interview protocols suggest that the use of DSM-IV based interviews tend to result in somewhat higher rates of substance abuse, but not of dependence (12,26,27).

To assess the extent to which the difference in the estimated rates of illicit drug abuse and dependence can be the result of differences in the study methods, we need to compare the prevalence rates of cohorts similar on year of assessment and age of risk. The report of the 1987 study shows lifetime prevalence rates of 1.8% and 0.6% for respondents 17 to 39 years old and 40 to 68 years old, respectively (16). When we focus on the respondents 27 to 49 years old in our study and compute the percentage that reported an onset of abuse or dependence 10 years earlier (i.e., when they were 17 to 39 years old) a comparison that matches with the 1987 17 to 39 years old cohort on year of assessment and age of risk the estimate from our data is 2.9% compared to the 1987 estimate of 1.8%. It seems that some of the difference of the rates can be

Table V

Past year use of health services by health care sector among respondents with past year DSM-IV alcohol and illicit drug abuse or dependence, Puerto Rico household population 15-64 years, 1997-1998 (n = 4,709)

	All Substances		Alcohol		Illicit Drugs	
	weighted %	SE	weighted %	SE	weighted %	SE
Used any sector	13.0	3.0	11.9	3.2	23.9	5.2
Used general sector	8.7	2.7	9.5	3.1	10.6	3.9
Used specialty sector	6.9	1.5	5.0	1.4	17.5	4.4
Used self-help sector	1.7	0.7	1.6	0.8	5.6	2.5

attributed to differences in study methods, yet a considerable portion of the increased rate of our study cannot be accounted by differences in methods. School surveys of drug use among adolescents have also shown steady increases in the use of illicit drugs throughout the 1990s (28). Thus, we believe that the prevalence of illicit drug use disorders increased in Puerto Rico from 1987 to 1997.

The lifetime prevalence of alcohol abuse or dependence estimated in this study (13.1%) is also very similar to the rate of lifetime alcohol abuse or dependence estimated in the U.S. general household population in 1991-92 (14.1%) (29). However, our estimate of lifetime illicit drug abuse (4.3%) is lower than the corresponding estimate for the U.S. population (7.5%), although the corresponding estimates of past year illicit drug abuse or dependence are not quite as different (1.3% vs. 1.8%) (30). A lower rate of illicit drug abuse and dependence in Puerto Rico than in the U.S. is consistent with several other studies of drug use in Puerto Rico (28,31), but inconsistent with public opinion and widespread beliefs about an exceedingly high prevalence of illicit drug abuse in Puerto Rico. Local press stories have quoted figures of over 150,000 currently addicted individuals in Puerto Rico (32). These figures represent a past year prevalence of over 6.3% among the population 15 to 64 years old, a rate five times higher than the rate estimated in our study (1.3%) and more than 3.5 times higher than the corresponding estimate for the U.S. (1.8%). Although our estimate may be biased downward by the under-reporting of drug use in household surveys, other indicators of drug abuse such as drug overdose deaths and property crime (33) do not support a rate as high as 6.3%.

The rates of substance use disorders estimated in our study must not be considered low. To place the potential health and social burdens of substance use disorders in context, it is useful to compare the lifetime prevalence rates estimated in this study with the lifetime prevalence rates of other psychiatric disorders estimated for the population of Puerto Rico. Avilés, Canino and Rubio-Stipec have published projections of lifetime psychiatric psychopathology for the population of Puerto Rico (34). In their projections, 13.9% of the population 17 to 64 years old in the year 2000 would have been affected by psychiatric disorders excluding simple and social phobias and substance use disorders. In contrast, our study estimates that a slightly higher proportion of the population of Puerto Rico (14.7%), has been affected by substance use disorders alone.

Risk of alcohol abuse and dependence increased significantly with increases in annual family income. Although not statistically significant, there was also a tendency for rates of alcohol abuse to increase with increases in educational level. However, none of these associations were present in the case of drug abuse and dependence. This finding was unexpected since alcohol abuse has been found in previous studies either not to be associated with measures of socio-economic status or to be associated with lower socio-economic status (15). We examined the effects of the post-stratification weight adjustments that were made to compensate for the lower participation rates of respondents living in block groups with a higher socio-economic index scores. Analyses conducted without these weight adjustments showed the same patterns of associations. The analyses were also conducted after excluding persons 17 to 24 years old who might not be able to report family income accurately and the positive association of family income with alcohol abuse or dependence persisted. Further studies of alcohol use disorders in Puerto Rico will be needed to ascertain if this finding replicates or if it might have been an artifact of some study procedure.

The age and gender variations in drug abuse or dependence found in this study are largely consistent with previous epidemiological research (30). The risk of illicit drug abuse increased with age, peaked in the cohort 25 to 34 years old, and decreased among older cohorts, particularly in the oldest cohort of persons 55 to 64 years old. The phenomenon of younger cohorts exhibiting higher rates of drug use and abuse has also been noted in the U.S. (35,37) and might be one of the reasons why drug abuse estimates in Puerto Rico from the 1987 study to the present study have tended to converge with U.S. estimates.

Nevertheless, two general epidemiological observations must be made about the association of age with risk of drug use disorders in cross-sectional studies. Cross-sectional studies survey the survivors of each birth cohort. Although drug-related mortality affects drug users in all the age cohorts, the cumulative effect of attrition increases as birth cohorts age. Thus, the lower lifetime prevalence of drug use disorders observed among the two oldest cohorts might be due partly to premature mortality as a sequelae of drug dependence. The mortality rates of hard core drug users in Puerto Rico have been found to be approximately 10 times higher than the risk of mortality of similar age and gender cohorts in the general population (38).

In addition to the cumulative effects of drug-related mortality, older cohorts also exhibit the cumulative effects of transitions from drug use to drug abuse. Kandel and others have shown that the probability of initiating drug use increases with age up until approximately age 35, at which point the risk of drug use initiation drops sharply (39,40,41). Drug abuse and dependence is thought to follow this same pattern of age-at-risk with a lag period of some years (42). Thus, the youngest cohort (15 to 24 years old) might had just started to enter the at-risk period and thus showed a lower rate of disorders than the older cohort of 25 to 34 years old. With passing time, the experience of the younger cohort may prove to be more like the experience of the older cohort, until drug-related excess mortality accumulates and drops in the rates of lifetime disorders start to show up.

We also found alcohol and drug use disorders to be associated with other psychiatric conditions, as well as with each other. The comorbidity results add to the body of evidence that underscores the need to screen for and treat all co-occurring disorders in integrated systems of care (21).

Only a minority of individuals with substance use disorders reported receiving services for their alcohol or drug problems. The use of services was particularly low among individuals with an alcohol abuse or dependence disorder. This finding is consistent with previous studies on substance abuse and other psychopathologies (25,43). Research on service utilization has tended to emphasize the study of the individual's predisposition to use services and other intraindividual factors (44). Nevertheless, lack of service availability might also have exerted an influence over the rates of utilization found in this study. A survey of substance abuse service providers that was conducted around the same time of the present study, estimated an average capacity utilization of 86% (45). Such a high rate of capacity utilization means that substance abusers were already using what specialty services were available. These data further suggest that service utilization is not likely to increase significantly without first increasing the availability of substance abuse treatment. Efforts to increase service use by motivating affected individuals to seek help (i.e., increasing demand) without concomitant increases in the availability of services (i.e., increasing supply) are not likely to prove effective and might result in lengthening waiting periods and further discouraging substance abusers from seeking care. At the time of our survey the reform of Puerto Ricos health system for the medically indigent population was still in its implementation stages. Thus, it remains to be seen whether the shift from publicly operated clinics to private, managed care facilities will have an effect on the availability and access to care for individuals with substance use disorders.

Some of the limitations of this study merit comment. Given the sensitive nature of questions about illicit drug use, it is likely that reports of illicit drug use were biased downward. To increase the privacy and anonymity of the interview we conducted the interviews over the telephone. In addition, a validity sub-study to compare self-reports of drug use with toxicological tests was conducted as part of this study. The results suggest that light drug users were unlikely to disclose their drug use in the study interview but that the self-reports of respondents at risk of substance use disorders were reasonably accurate. Methods to increase the willingness of respondents to disclose their use of drugs are needed. Several studies have shown that drug use reports are sensitive to interview mode effects (46,47). Specifically, it has been shown that self-administered questionnaires yield higher rates of drug use reports than face-to-face interviews (48-50). However, self-administered questionnaires have limited use for studies of drug use disorders due to the complicated skip patterns of a diagnostic interview and the literacy requirements of a self-administered questionnaire. Recent computational developments now allow the integration of audio to computer assisted self-interviews (i.e., Audio CASI systems). The availability of portable computers and Audio CASI systems could help overcome the limitations of self-administered questionnaires and have been proposed by several researchers (51). Studies of the acceptability of Audio CASI systems in the general population (52) and of the validity of the collected data are needed to examine if this new technology is useful for the epidemiological study of drug use disorders.

During the recently concluded twentieth century, Puerto Rico transitioned epidemiologically from a population burdened by infectious agents to a population for the most part affected by chronic diseases such as cancer, cardiovascular disease, and substance abuse. The etiologies of most chronic conditions share sociobehavioral risk factors and social determinants. In this new disease context, traditional disease surveillance systems based on reports of patients presenting to treatment will continue to be of public health importance but will prove to be increasingly deficient in the absence of systems of population surveillance. A program of continuous monitoring of the

populations alcohol and drug using behaviors and disorders is critical to further our understanding of these health conditions, assist in establishing effective policies and realistic objectives, and periodically check on the progress achieved.

Resumen

Presentamos los hallazgos sobre desórdenes por uso de substancias examinados en una muestra de 4,709 personas de 15 a 64 años. Uso de alcohol alguna vez fue informado por el 77.2%; el 10.7% informó uso de drogas ilícitas alguna vez. El 14.7% de la muestra cumplió con criterios de desorden de substancia alguna vez, y el 4.9% durante el pasado año. Las tasas de desórdenes fueron 13.1% por alcohol y 4.1% por drogas ilícitas, alguna vez; y 4.3% y 1.3% durante el pasado año, respectivamente. Los desórdenes por alcohol estuvieron asociados a sexo masculino, ingreso familiar alto, estar empleado, y estar casado. Los desórdenes por drogas estuvieron asociados a sexo masculino y edad joven. Sólo el 13.0% de las personas con desorden utilizó servicios para atender su condición. Será necesario contar con un programa de vigilancia continua de los desórdenes de substancias para establecer y monitorear políticas públicas efectivas.

Palabras Clave:
Desórdenes de uso de substancias, Puerto Rico, Estudios de comunidad

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The most commonly reported adverse events are transient local pain, swelling, and/or effusion in the injected knee (2.2% of injections in clinical trials). In some cases, these symptoms have been extensive. Other side effects such as rash have been reported rarely. SYNVISC is contraindicated in patients with known hypersensitivity to hyaluronan products or patients with infections in or around the knee. Use caution when using SYNVISC in patients allergic to avian proteins, feathers, and egg products or who have evidence of venous or lymphatic stasis in the leg to be treated. The results of repeat use have not been established. Strict adherence to aseptic technique must be followed to avoid joint infection.

**Retrospective study of Canadian clinical experience; Lussier et al reviewed medical charts of 336 patients aged 22-92 (458 knees) with a history of knee OA who received SYNVISC (3 injections one week apart), and evaluated overall treatment response by medial x-ray grades I-IV. Efficacy evaluated on a 5-point scale: much better, better, same, worse, much worse. Number of patients: grade I (N=68), grade II (N=138), grade III (N=180), grade IV (N=57). Results in radiologic grade IV patients: 58% had better or much better response. The incidence of local injection site events was 2.7% of injections.*

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BRIEF SUMMARY FOR THE PHYSICIAN (CONSULT PACKAGE INSERT FOR FULL PRODUCT INFORMATION)

CAUTION: Federal Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

INDICATIONS Synvisc is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

CONTRAINDICATIONS • Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations. • Do not inject Synvisc in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

WARNINGS • Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence. • Do not inject Synvisc extra-articularly or into the synovial tissues and capsule. Local and systemic adverse events, generally in the area of the injection, have occurred following extra-articular injection of Synvisc. • Intravascular injections of Synvisc may cause systemic adverse events.

PRECAUTIONS General • The effectiveness of a single treatment cycle of less than three injections of Synvisc has not been established. • The safety and effectiveness of Synvisc in locations other than the knee and for conditions other than osteoarthritis have not been established. • Do not inject anesthetics or other medications into the knee joint during Synvisc therapy. Such medications may dilute Synvisc and affect its safety and effectiveness. • Use caution when injecting Synvisc into patients who are allergic to avian proteins, feathers, and egg products. • The safety and effectiveness of Synvisc in severely inflamed knee joints have not been established. • Strict aseptic administration technique must be followed. • STERILE CONTENTS. The syringe is intended for single use. The contents of the syringe must be used immediately after its packaging is opened. Discard any unused Synvisc. • Do not use Synvisc if package is opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). DO NOT FREEZE. • Remove synovial fluid or effusion before each Synvisc injection. • Synvisc should be used with caution when there is evidence of lymphatic or venous stasis in that leg.

Information for Patients • Provide patients with a copy of the Patient Labeling prior to use. • Transient pain, swelling and/or effusion of the injected joint may occur after intra-articular injection of Synvisc. In some cases the effusion may be considerable and can cause pronounced pain; cases where swelling is extensive should be discussed with the physician. • As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged weight-bearing activities such as jogging or tennis following the intra-articular injection. • The safety and effectiveness of repeat treatment cycles of Synvisc have not been established. • The packaging of this product contains dry natural rubber latex.

Use in Specific Populations • Pregnancy: The safety and effectiveness of Synvisc have not been established in pregnant women. • **Nursing mothers:** It is not known if Synvisc is excreted in human milk. The safety and effectiveness of Synvisc have not been established in lactating women. • The safety and effectiveness of Synvisc have not been established in children.

ADVERSE EVENTS

Adverse Events Involving the Injected Joint

Clinical Trials: A total of 511 patients (559 knees) received 1771 injections in seven clinical trials of Synvisc. There were 39 reports in 37 patients (2.2% of injections, 7.2% of patients) of knee pain and/or swelling after these injections. Ten patients (10 knees) were treated with arthrocentesis and removal of joint effusion. Two additional patients (two knees) received treatment with intra-articular steroids. Two patients (two knees) received NSAIDs. One of these patients also received arthrocentesis. One patient was treated with arthroscopy. The remaining patients with adverse events localized to the knee received no treatment or only analgesics.

Postmarket Experience: The most common adverse events reported have been pain, swelling and/or effusion in the injected knee. In some cases the effusion was considerable and caused pronounced pain. In some instances, patients have presented with knees that were tender, warm and red. It is important to rule out infection or crystalline arthropathies in such cases. Synovial fluid aspirates of varying volumes have revealed a range of cell counts, from very few to over 50,000 cells/mm³. Reported treatments included symptomatic therapy (e.g., rest, ice, heat, elevation, simple analgesics and NSAIDs) and/or arthrocentesis. Intra-articular corticosteroids have been used when infection was excluded. Rarely, arthroscopy has been performed. The occurrence of post-injection effusion may be associated with patient history of effusion, advanced stage of disease and/or the number of injections a patient receives. Reactions generally abate within a few days. Clinical benefit from the treatment may still occur after such reactions.

Intra-articular infections did not occur in any of the clinical trials and have been reported only rarely during clinical use of Synvisc.

OTHER ADVERSE EVENTS

Clinical Trials: In three concurrently controlled clinical trials with a total of 112 patients who received Synvisc and 110 patients who received either saline or arthrocentesis, there were no statistically significant differences in the numbers or types of adverse events between the group of patients that received Synvisc and the group that received control treatments. Systemic adverse events each occurred in 10 (2.0%) of the Synvisc-treated patients. There was one case each of rash (thorax and back) and itching of the skin following Synvisc injections in these studies. These symptoms did not recur when these patients received additional Synvisc injections. The remaining generalized adverse events reported were calf cramps, hemorrhoid problems, ankle edema, muscle pain, tonsillitis with nausea, tachyarrhythmia, phlebitis with varicosities and low back sprain.

Postmarket Experience: Other adverse events reported include: rash, *hives*, itching, *fever*, nausea, *headache*, *dizziness*, *chills*, muscle cramps, *paresthesia*, peripheral edema, *malaise*, *respiratory difficulties*, *flushing* and *facial swelling*. There have been rare reports of *thrombocytopenia* coincident with Synvisc injection. These medical events occurred under circumstances where causal relationship to Synvisc is uncertain. (Adverse events reported *only* in worldwide postmarketing experience, not seen in clinical trials, are considered more rare and are *italicized*.)

DETAILED DEVICE DESCRIPTION

Each syringe of Synvisc contains:

Hylan polymers (hylan A + hylan B)	16 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate	0.32 mg
Sodium dihydrogen phosphate monohydrate	0.08 mg
Water for injection	q.s. to 2.0 mL

HOW SUPPLIED

Synvisc is supplied in a 2.25 mL glass syringe containing 2 mL Synvisc.

Product Number: 0008-9149-02 3 disposable syringes

The contents of the syringe are sterile and nonpyrogenic.

DIRECTIONS FOR USE

Synvisc is administered by intra-articular injection once a week (one week apart) for a total of three injections.

Precaution: Do not use Synvisc if the package has been opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). DO NOT FREEZE.

Precaution: Strict aseptic administration technique must be followed.

Precaution: Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.

Precaution: Remove synovial fluid or effusion before each Synvisc injection.

Do not use the same syringe for removing synovial fluid and for injecting Synvisc, but the same needle should be used.

Take particular care to remove the tip cap of the syringe and needle aseptically.

Inject Synvisc into the knee joint through an 18- to 22-gauge needle.

To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.

Do not inject anesthetics or any other medications intra-articularly into the knee while administering Synvisc therapy. This may dilute Synvisc and affect its safety and effectiveness.

Precaution: The syringe containing Synvisc is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging. Inject the full 2 mL in one knee only. If treatment is bilateral, a separate syringe must be used for each knee. Discard any unused Synvisc.

This brief summary is based upon the current circular, CI 6082-2, revised September 29, 2000.

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Reporte de Caso:

Presacral Neuroblastoma in a Child: A Case Report

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Abstract

Presacral location of neuroblastoma is rare. Resection entails an abdomino-sacral approach. This case report discusses clinical, imaging and successful surgical management of a presacral neuroblastoma in a one-year-old male child.

Neuroblastoma is the most common extracranial solid tumor of childhood and the most common congenital malignant tumor of infancy with approximately one-third occurring within the first year of life.[1-3] Pelvic origin is extremely rare accounting for approximately 2 to 4% of all neuroblastomas.[4] Within this location, the majority of neuroblastomas arise from the organ of Zukerkandl found in the presacral region. Presacral neuroblastomas typically present asymptomatically with a palpable mass or bowel and urinary symptom.[2] This case report discusses the clinical, imaging and surgical management of a presacral neuroblastoma in a one-year-old male.

Case History

This is the case of a one-year-old Hispanic boy without history of systemic illness born to a 29 year old Grava 5, Para 5, Aborto 0 mother, after 39 weeks of gestation. Mother reported that the patient appeared healthy since birth with the exception of periodic episodes of constipation. A few days prior to admission the mother noticed that the patient was severely constipated with abdominal tenderness and urinary retention. The child was admitted to the local hospital where physical examination revealed abdominal tenderness and a palpable bladder. Catheterization was performed and 350 cc of urine was obtained. Patient was transferred to the University Pediatric Hospital for further management. A water-soluble contrast enema demonstrated the rectum displaced to the right and anteriorly by a large sacral mass with poor distinction of the recto-sigmoid due to compression. Pelvic sonogram revealed a solid mass located in the inferior aspect of the pelvis, posterior to the bladder (see Figure 1). Computerized tomography revealed bilateral hydronephrosis and a presacral 4.5 cm x 4.5 cm solid mass without lymphadenopathy. Magnetic resonance imaging

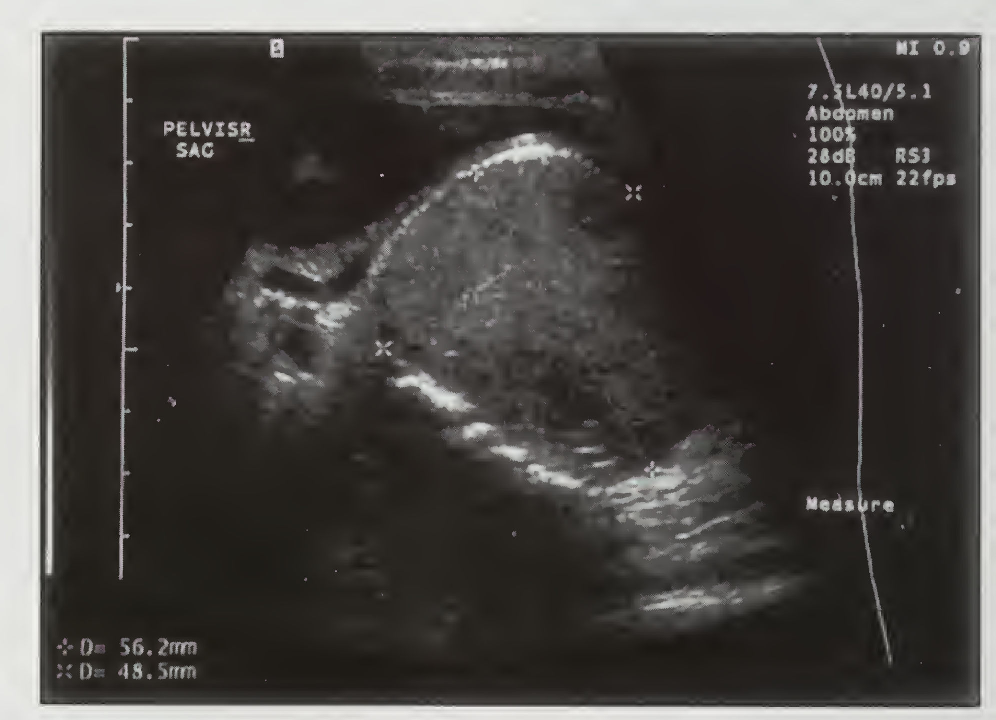


Figure 1:
Ultrasound showing a solid pelvic mass displacing the bladder anteriorly.

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confirmed the size and location of the presacral mass (see Figure 2). Bone scan indicated no evidence of metastatic disease. With a working diagnosis of a type IV (Altman's classification) sacrococcygeal teratoma the child was schedule for surgery.[5]

After stabilization abdomino-sacral resection of the mass was performed. The abdominal procedure consisted of a transverse infraumbilical incision upon which the retroperitoneal area was entered between the colon and the left ureter near the midline identifying the mass. Ureter, vas deferens and gonadal vessels on the left side were identified and preserved. Small bowel was retracted cephalically and the bladder was retracted caudally. Blunt dissection was used to separate the mass from adjacent tissue. The patient was then rotated to the prone position and a longitudinal sagittal incision was made at the midline down to the sacral bone. The coccyx was removed. The mass was identified, its posterior attachments released and completely extracted through the sacral incision. A Penrose drain was left at the pelvic area and the abdomen closed.

A specimen of a dark tan, soft-to-rubbery tissue mass that measured 5.3 x 4.5 x 5 cm was collected. Externally it was smooth and lobulated with irregular areas on section. It presented a reddish and whitish granular cut surface. The pathology report issued a diagnosis of a differentiating neuroblastoma.



Figure 2:

Magnetic Resonance sagittal image showing the presacral solid mass originating from the sacral vertebras and displacing the bladder (Foley balloon in place – white arrow) and rectum (black arrow) anteriorly.

Discussion

Neuroblastomas comprise almost 50% of all neonatal malignant tumors and 5 to 8% of all abdominal tumors in newborns. Approximately 50% of neuroblastomas occur within the first two-years of life and 90% are found by the time the child reaches eight years of age.[1] The tumor is derived from embryonal neural crest tissue. The sites of origin are sympathetic nervous tissue, most commonly the adrenal glands, retroperitoneum and mediastinum. Majority of patients excretes catecholamines and their breakdown products in the urine. Systemic symptoms are common and include fever, weight loss, failure to thrive, anemia, and hypertension. Most children have metastases to bone, bone marrow, lymph nodes, liver, and subcutaneous tissue when diagnosed. Neuroblastomas are associated with hydrops fetalis, hepatomegaly, paralysis, cardiomegaly, hypoglycemia, multiple bluish subcutaneous nodules and Horner's syndrome. Furthermore, fetal neuroblastomas are the only solid tumor that may lead to placental metastasis.[6]

Prognosis of neuroblastomas varies with age, location and characteristics of the tumor. Overall survival rate is 40 to 50%. This rate increases to 75% for infants, but decreases to 20% for those children over two-years of age. Interestingly, undifferentiated (grade 3) or partially differentiated (grade 2) neuroblastomas are more prevalent in young infants compared to children older than six-month.[7] Lack of differentiation is not necessarily associated with a poor prognosis given the high survival rates seen in young infants. Localized and completely resected neuroblastomas are associated with a better than 95% survival rate. Survival rate drops to 20% in children with metastatic disease. Metastatic disease, however, is not necessarily associated with a poor prognosis. Infants younger than one-year of age that have bone marrow, liver, and skin metastasis have a survival rate greater than 80%, even in the absence of treatment. Neuroblastomas have the unique ability to undergo differentiation to a benign form known as ganglioneuroblastoma. Incidence of ganglioneuroblastomas in infants under the age of six-month is a mere 1%, whereas in children older than six-month of age rises to 38%.

Neuroblastomas of pelvic origin, as previously mentioned, are extremely rare accounting for only 2 to 4% of all cases. They typically present as asymptomatic palpable masses or with bowel or urinary compressive symptoms. Infants presenting with urinary retention must be evaluated for the presence of presacral neoplasm.[8] Pelvic neuroblastomas are commonly localized and are typically associated with a better prognosis compared to abdominal neuroblastoma.[9] Chief complaints of the present case study involved episodes of constipation associated with urinary retention. Prognosis for our patient is based on several variables both in favor and against a good outcome. His young age, the origin of a pelvic neuroblastoma with its typical localized behavior, low-grade differentiation and successful complete resection of the presacral mass support a good prognosis. The most common neoplasms that arise in the presacral region is the sacrococcygeal teratoma initially thought to be the preoperative diagnosis in this case. Other diagnostic possibilities included the Currarino triad, tumors of neural origin and rhabdomyosarcoma.[10]

Resumen

La localización presacral del tumor conocido como Neuroblastoma es extremadamente rara.
Su remoción quirúrgica entiende un abordaje abdomino-sacral.
Este caso único presenta y discute los hallazgos clínicos, imágenes obtenidas y el manejo quirúrgico de un neuroblastoma presacral en un varón de un año de edad.

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Reporte de Caso:

Carcinoid tumor in Puerto Rico; two case reports

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Introduction

Carcinoid tumors had an incidence of one to two cases per 100,000 people in U.S. In Puerto Rico this incidence has not been reported. Few cases of carcinoid tumor present with pleural effusions but in our case reports we found this finding in the two cases. The release of serotonin and vasoactive substances produce the manifestation of episodic flushing, wheezing, diarrhea, and right-side heart valvuloplasty. Episodic chronic diarrhea is an early marker of carcinoid tumors.

Here we report the presentation of two cases of carcinoid tumor from the west part of the island of Puerto Rico.

Case reports

Patient 1: A 64 year old man was admitted on September 1999 with hypertension, chronic atrial fibrillation who had intermittent diarrhea with episodes of constipation, and dyspepsia for five years previous to admission. One day prior to admission he had severe epigastric pain. The patient had a history of cholelithiasis. He denied fever, vomiting or black stools.

On physical examination, there was scleral icterus. There was a regular rate and a systolic ejection murmur best heard at the left sternal border grade II/VI. There was no jugular venous distention of the neck veins at 451. There was expiratory wheezing at right lung base. There was no hepatosplenomegaly and no palpable abdominal masses. The skin in the anterior chest area presented with flushing. A CT scan of the chest showed a moderate pericardial effusion. An abdominal sonogram showed evidence of metastatic disease. The hydroxyindoleacetic acid (HIAA) in urine (normal <or= 6 mg/d) was 60 mg/24 hrs. A liver and spleen scan showed a large defect in the superior aspect of the right liver pole and a small defect in the inferior aspect of the right liver lobe. The echo 2 D demonstrated a pericardial thickening with effusions. A liver biopsy showed a carcinoid tumor.

The pericardium was drained through a window and he received treatment with octreotide. Now after three years the first patient is feeling well with decrease episodes of diarrhea and flushing. See figure 1 for his biopsy specimen.

Patient 2: A 75 year old woman with coronary artery disease and hypothyroidism with intermittent diarrhea for four years prior to being admitted on October 2000. Diarrhea was greenish in color and accompanied by abdominal pain. She denied skin flushing. An aunt had cancer of the liver and a sibling had cancer of the colon. One month previous to admission the patient had an outpatient CT scan of the abdomen that showed a carcinoid tumor.

On physical examination, the

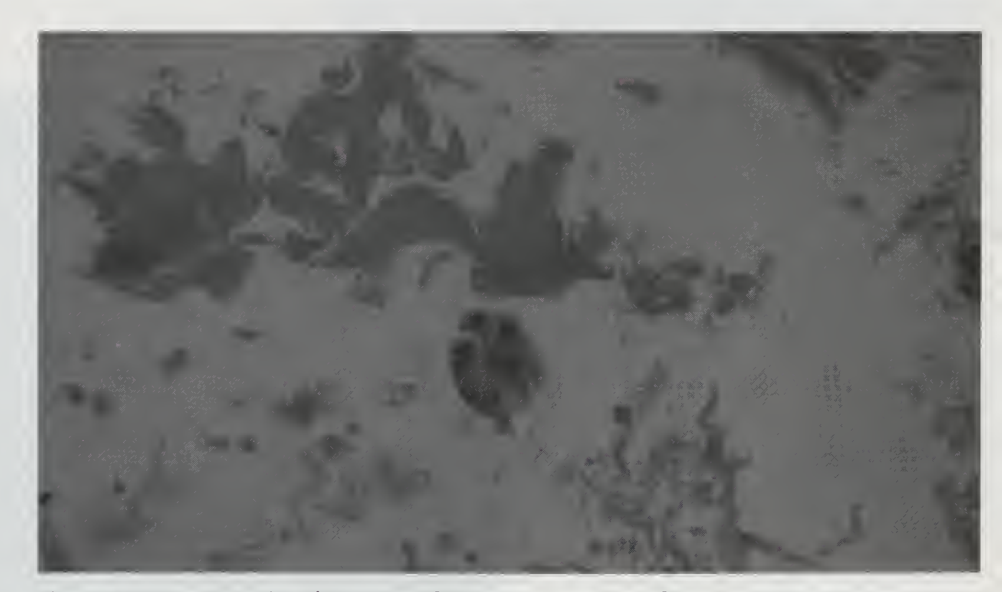


Figure 1: Metastasis of carcinoid tumor to pericardium in patient one.

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Figure 2A: Carcinoid tumor in the intestines of patient two.

temperature was 36.61 C, the blood pressure was 136/100 mmHg., the respiratory rate was 20/minutes and the pulse was regular at 121/min. The patient was alert but there were bibasilar inspiratory crackles over the posterior aspect of her chest. The abdomen had no bowel sounds and was distended and tympanic. No flushing of the skin was observed. Her total leucocyte count was 8.5 x 10^3 /mm^3, hemoglobin 11.8 g/dL, hematocrit 33%, sodium 142 meq/L, potassium 3 meq/L, chloride 102 meq/L, carbon dioxide content 26 meq/L, urea nitrogen 12 mg/dL, creatinine 1.2 mg/dL and the glucose was 204 mg/dL. The chest x-ray showed a left pleural effusion. A plain film of the abdomen suggested an ileus. The HIAA in urine was 39.5 mg. /24 hrs. The liver biopsy showed a metastatic carcinoid tumor and a biopsy of the peritoneal wall demonstrated a carcinoid tumor. The patient had surgery for intestinal obstruction but in spite of being treated with octreotide 100 mg subcutaneous every eight hour and streptozime the patient died 13 days after her admission. See figure 2 for her biopsy specimen.

Conclusions

The differential diagnosis of a carcinoid tumor should come to our minds when we deal with patients with unexplained chronic episodic diarrhea. The diagnosis of a carcinoid tumor is usually made after a metastasis has occurred. After we rule out common conditions that produce chronic diarrhea we should consider an HIAA test in the urine. Although it has not been proven that early detection of carcinoid tumors will affect mortality, the octreotide or streptozotime seen to provide effective palliation



Figure 2B: Metastasis of carcinoid tumor to the peritoneum of patient two.

Acknowledgements

I would like to thanks Dr. José Ramírez Rivera, Dr. Fausto Lugo and Dr. Francisco Jaume for their expert guidance and invaluable advices during the planning of this study.

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Reporte de Caso:

St. Segment Elevation: Is it a possible infart?

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Abstract

In patients with acute substernal pain seen at Emergency Departments, ST segment elevations are considered the hallmark of an acute myocardial infarct. Acute substernal pain associated with ST segment elevations is the inclusion criteria for thrombolytic therapy. However, there are other conditions, which may present with ST segment elevation in which thrombolytic therapy is not indicated. Acute pericarditis and ECG variants of normal must also be considered in the differential diagnosis. Three cases are presented that illustrate this ECG presentation. It is of paramount importance, that the Emergency Department physician who does the triage for these patients be able to identify the various causes of ST segment elevations.

Key words: myocardial infarction, myocardial ischemia, normal variant, pericarditis, ST segment elevation.

Introduction

Patients with acute substernal pain who arrive at the Emergency Department with ST segment elevations are usually considered to have an acute myocardial infarction. Because treatment of closing coronary arteries is urgent, acute substernal pain associated with ST segment elevation is the only inclusion criteria required for thrombolytic therapy (1). The three cases described below illustrate this diagnostic problem and therapeutic dilemma.

Case Reports

CASE 1

A healthy 30-year old man suddenly developed acute retrosternal oppressive chest pain while at rest. His father had died at 38 years of age due to a myocardial infarct. The patient's electrocardiogram (ECG) showed concave ST segment elevation of 2 mm in lead V4 and 1 mm elevation in lead V5 (Figure 1). He received intravenous (IV) nitroglycerin without response. Because the pain did not abate and ST segment elevations persisted thrombolytic therapy and IV heparin were administered. Creatinine Kinase-MB (CK-MB) every 8 hours for three times and cardiac Troponin I did not indicate myocardial injury. An echocardiogram showed normal left ventricular

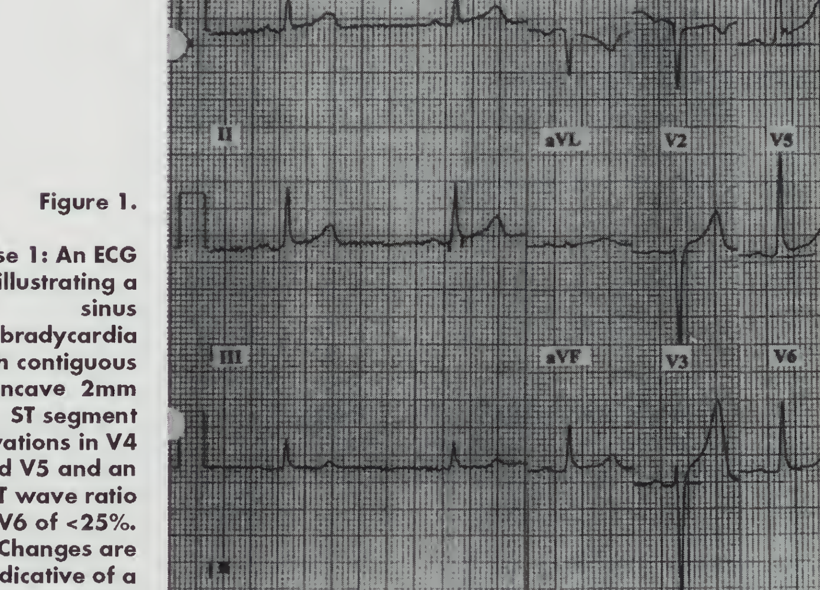


Figure 1.

Case 1: An ECG illustrating a sinus bradycardia with contiguous concave 2mm ST segment elevations in V4 and V5 and an ST/T wave ratio in V6 of <25%. Changes are indicative of a normal variant.

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Presented in part at the Puerto Rico Associates' Meeting of the American College of Physicians-American Society of Internal Medicine. Saturday, May 22, 1999, Tropimar Beach Club & Convention Center, Isla Verde, Puerto Rico

wall motions and a normal ejection fraction. A reevaluation of the ECG and serial tracings showed the ECG changes to be consistent with a normal variant. The pain was thought to originate in the chest wall. A stress test was negative for ischemia.

CASE 2

A healthy 20-year old man suddenly developed oppressive retrosternal chest pain while at rest. Three weeks prior to admission he had fever and myalgia compatible with a viral syndrome. He smoked less than a pack of cigarettes a day and used alcohol beverages sparingly. His parents were healthy, no one in his immediate family had coronary artery disease. On admission he was afebrile and the physical examination was unremarkable. The ECG showed diffuse ST elevations with a concave shape measuring 1mm in lead I, 1.5mm in lead II, and at least 2mm in V4 to V6 (Figure 2). There was no displacement of PR segment. He was admitted to Intensive Care Unit (ICU) but did not received thrombolytic therapy. The CK-MB increased to 15% of the to CK and Troponin I increased to 7.2 ng/dl suggesting myocardial injury. The echocardiogram and myocardial perfusion scans were normal. A clinical toxicology screen was negative for cocaine,. The third day after admission ST segments had partially returned to the baseline and the T waves in V5 and V6 had become terminally inverted. The clinical picture and ECG serial changes were thought compatible with acute pericarditis associated with epicardial injury.

CASE 3

A man age 59 with diabetes and hypertension was well until he was awakened by crushing substernal pain and shortness of breath. The physical examination was

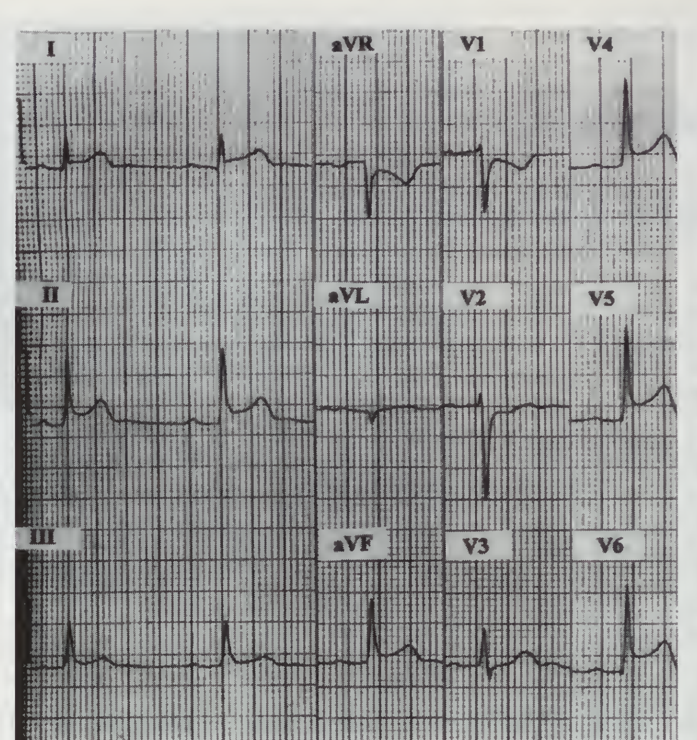


Figure 2.

Case 2: An ECG showing a sinus rhythm with ST segment elevations in leads I,II,III, AVF and V4 to V6. There are no reciprocal changes in limb leads and no displacement of the PR segment. The ST/T ratio in V6 is >25%. Changes are compatible with acute pericarditis.

unremarkable. ST segment elevation of less than 1mm in lead II, 1mm in V2 and V3 were evident in the initial ECG. There was also straigntening of ST segments in V2 to V5. The ST segment elevations did not fulfill the criteria for thrombolytic therapy. Pain did notresolve with intravenous nitroglycerin and six hours later there was a upward straightening of the ST segment measuring of 1mm in lead I, V3,V4,V5, and 2mm in V2 (Figure 3). He was transferred to the ICU and thrombolytic therapy was then administered.

An echocardiogram after the administration of thrombolytic therapy, while still having pain, showed a left ventricular ejection fraction of 35% with anteroseptal, apical, and inferolateral hypokinesia. CB-MB and Troponin I did not show evidence of myocardial injury. Coronary angiography performed 3 days after admission demonstrated three-vessel disease with left ventricular ejection fraction of 65%. Subsequently, a coronary artery bypass was performed. He was seen in March and was asymtomatic and well. An infarct may have been avoided with the judicious use of thrombolytic therapy.

Discussion

When considering thrombolytic therapy, the ECG remains the primary method of screening patients for myocardial ischemia. Two or more risk factors associated with persistent pain, prior MI, dyspnea, hypotension, a third heart sound and crackles on physical examination may strengthen the significance of the initial ECG interpretation. Echocardiographic screening demonstrating regional wall motions abnormalities, such as cardiac serum makers and myocardial perfusion imaging, are useful, but their results are not immediatelly available and consequently they play a secondary roll in determining which patients should receive thrombolytic therapy(3).

The three specific criteria used for the initiation of thrombolytic therapy are: ST segment elevations that are

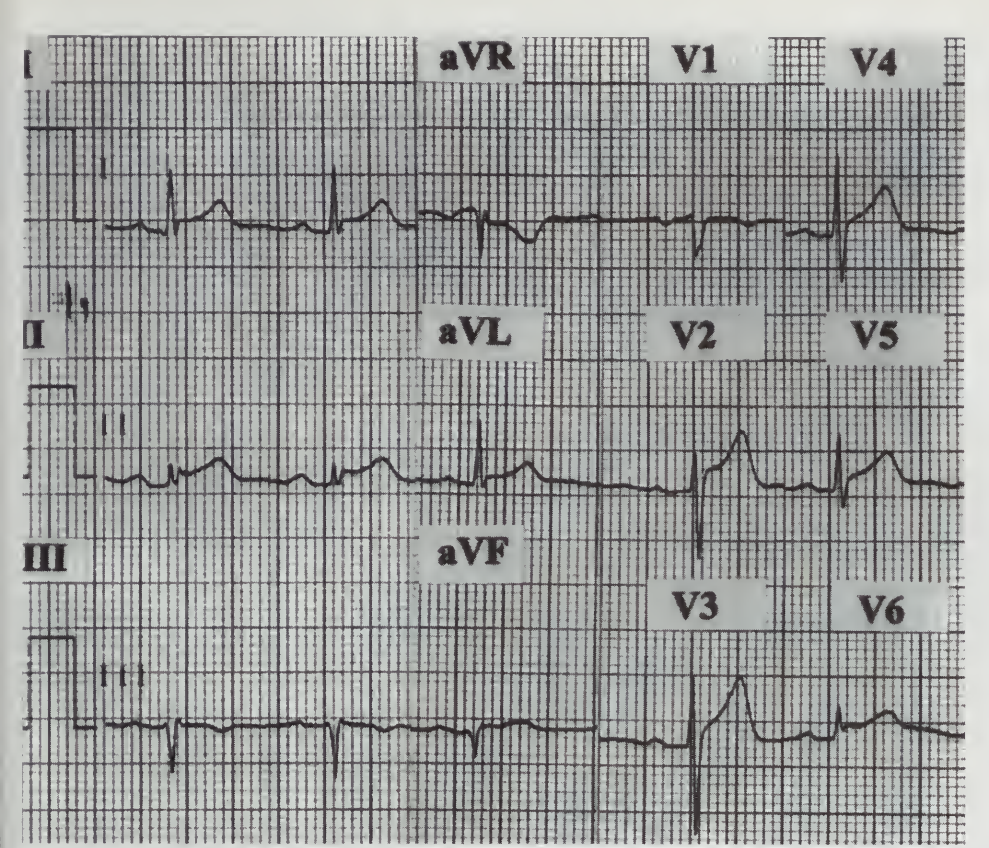


Figure 3. Case 3: An ECG demonstrating a sinus rhythm with straightening of the ST segments and 2mm elevation in V2 and V3 and 1mm ST segment elevation in V5 to V6. Changes are suggestive of acute ischemic injury.

equal or greater than 1mm in two or more anatomically contiguous leads, 1mm ST elevation in limb leads or in V4 through V6, 2 mm ST segment elevation in V1 through V3, or a new onset of left bundle branch block (1).

The accurate measurement and assessment of ST segment elevations is, therefore important. (The reliable baseline for this measurement is a line drawn from the start of the P wave to the end of the T wave, the so-called PT baseline. The measurement should be taken 0.04 seconds after the J point, the end of the QRS) (3).

Eight elements of the ECG have some diagnostic value in differentiating normal variants from pericarditis and myocardial ischemia (Table 1). In normal variants a previous and serial tracing remain unchanged. The ST segment shape is concave and the ST/T ratio in V6 is < 25%(4). (The ST/T ratio in V6 is obtained by using the end of the PR segment as baseline and dividing the amplitude of the ST segment onset by the T wave maximal amplitude).

In acute pericarditis serial tracings evolve. Concave ST segment elevations are usually present in all leads except, obviosly, in aVR. In acute pericarditis the PR segment is displaced in 60% of the cases and the ST/T ratio is > 25%(5). The ST/T ratio in V6 is particularly useful in differentiating normal variants from acute pericarditis. As already indicated, the ratio is <25% in normal variants and > 25% in acute pericarditis.

In myocardial ischemia the serial tracings show evolution. The convex shape and/or upward straightening of the ST segment are highly suggestive of myocardial injury. ST reciprocal changes when present, are specific for myocardial injury and pathologic Q waves are indicative of necrosis but appear late (6).

Conclusion

When there is substernal pain, ST segment elevation may suggest the possibility of myocardial ischemia but other causes must be excluded. Physicians in Emergency Departments should have the skills to separate the concave shape of ST segments in a normal variant and acute pericarditis from myocardial ischemia. The convex ST shape and/or upward straightening of the ST segment highly suggestive of ischemia injury should also be recognized. The ST/T ratio in V6 clearly separates normal variants (>25%) from acute pericarditis (>25%) but it is variable in ischemic injury. Regional abnormalities in an echocardiogram may be helpful in demonstrating ischemia when the significance of the ST segment changes are in doubt.

Resumen

En pacientes con dolor retroesternal que son evaluados en Sala de Emergencia, elevación del segmento ST sugiere a un infarto agudo al miocardio. En efecto, dolor retroesternal asociado con elevación del segmento ST son los criterios de inclusión para terapia con agentes trombolíticos. En otras condiciones que también esten asociadas con elevación de ST el uso de agentes trombolíticos esta contraindicado. Pericarditis aguda y cambios electrocardiográficos que son una variante normal debe ser considerados en el diagnóstico diferencial. Se ilustran estos cambios electrocardiográficos en tres

pacientes. Es de gran importancia que los médicos que prestan servicios en Sala de Emergencia tengan las destrezas para identificar las condiciones que producen elevaciones del segmento ST.

TABLE 1

ECG ELEMENTS DIFFERENTIATING NORMAL VARIANTS FROM PERICARDITIS AND MYOCARDIAL ISCHEMIA

	NORMAL VARIANTS	PERICARDITIS	MYOCARDIAL ISCHEMIA
1. Previous Tracing	Unchanged*	Normal	Normal
2. Serial Tracing	Unchanged*	Evolve	Evolve
3. Localization (Leads)	V5, V6, I, AVL	All Leads*	Variable
4. ST Reciprocity	Absent	Absent	Present*
5. St Segment Shape	Concave	Concave	Convex or upward straightening*
6. Q Wave	Absent	Absent	Present*
7. PR Segment	Normal	Displaced	Normal
8. ST/T Ratio V6	<25%*	>25%*	Variable

* Diagnostically useful changes underlined

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Artículos de Revisión:

In Utero Demonstration of Aberrant Systemic Blood Supply in Lung Sequestration: A Case Report

Luis A. Izquierdo, MD[A, B], Victor H. Gonzalez-Quintero MD[A], Thomas Hortz MD[A], Lama Tolaymat MD[A], Massomeh Hahgayeh RDMS[B]

Abstract

Prenatal diagnosis of a potentially lethal condition as shown and confirmed with color flow Doppler; demonstration of an aberrant systemic blood supply.

Key Words
Lung sequestration, intrathoracic, color flow Doppler

Introduction

Appropriate prenatal diagnosis of fetal chest masses is of utmost importance. The diagnosis will allow for intervention aimed at prevention and reversal of hydrops fetalis and pulmonary hypoplasia (1.2).

The use of color Doppler ultrasonography has been shown to be an important tool in the diagnosis of chest masses such as right-sided diaphragmatic hernia as well as for lung sequestrations (2).

We will present and discuss a case of extralobar intrathoracic lung sequestration that was diagnosed by Two Dimensional ultrasound and confirmed by color Doppler examination.

Case Report

A 32-year-old G4P3 AB 0 at 33 weeks of gestation was referred to our unit for a second opinion ultrasound. The patient had been diagnosed with Non Immune Hydrop Fetalis and Tension Hydrothorax.

Targeted ultrasonography revealed a single intrauterine pregnancy with a Biparietal Diameter (BPD) of 79 mm, consistent with 32 weeks. The Head Circumference (HC) was 277 mm, consistent with 32.5 weeks. Abdominal Circumference (AC) was301 mm, consistent with 34.2 weeks. Femur Length (FL) was 66 mm, consistent with 33.5 weeks.

The anatomical survey revealed normal intracranial anatomy. There was evidence of minimal scalp edema. Facial anatomy was normal. On examination of the fetal chest, we found a left sided Tension Hydrothorax with two very small lungs (Figure 1). Adjacent to the left



Figure 1: Transverse view of the fetal chest demonstrating fetal hydrothorax with two very small lungs.

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lung an echogenic mass was seen. Echoes of this mass were similar to the lung tissue (Figure 2). Saggital examination of the chest demonstrated a mass on the left hemothorax separate from the lungs (Figure 3).

Color Doppler interrogation of the area demonstrated a vessel connecting directly from the descending aorta to the lung mass (Figure 4). Fetal echocardiogram revealed a normal fetal heart. The abdominal cavity showed minimal ascites and a normal anatomy.

Karyotyping was performed by amniocentesis. 46, XY results were obtained. At this point the option of fetal interventional procedures versus maternal corticosteroid administration and delivery was offered to the patient.



Figure 2: Transverse view of the fetal chest demonstrating the accessory lung mass. The echogenicity of this mass is similar to the lung tissue.



Figure 3: Sagital section of the fetal chest demonstrating a mass separate from the normal lung tissue.

Induction of labor with Misoprostol 50 gm q4h was performed. Spontaneous rupture of membranes occurred and cord prolapse ensued. Cesarean section was performed and a single living male child weighing 2717 gms (80th ile) with umbilical artery gases of PH 7.26 mm Hg, PO2 23 mm Hg, PCO2 74 mm Hg was delivered. Neonatology team stabilized fetus with thoracocentesis but X-rays showed severe pulmonary hypoplasia.

The neonate expired and a post mortem examination was performed (Figures 5) validating our prenatal diagnosis.

Discussion

Lung sequestration is a rare anomaly. A high index of suspicion and prompt in utero therapy is needed to attempt a reduction of the mortality rate (1,2).

The accessory lung is felt to originate from a separate outpouching of the foregut or a segment of developing lung that has lost its connection to the rest of the lung. If the accessory lobe arises before the formation of the pleura it will be surrounded by the same pleura as normal lung tissue and it will be referred to as intralobar. When the accessory lobe arises after the formation of pleura, it will have its own pleura and is referred to as extralobar (3).

Sonographically, the sequestered lung appears as an echogenic, nonpulsatile intrathoracic mass. Shifting of the mediastinum is commonly seen (1, 2) .

The perinatal mortality is almost 100% when associated with nonimmune hydrops fetalis (NIHF).



Figure 4: Sagital section of the fetal chest using color Doppler examination and demonstrating a vessel connecting the mass to the descending aorta.



Figure 5: Postmortem exam confirming the diagnosis.

The differential diagnosis of pulmonary sequestration includes mediastinal tumors, cystic adenomatoid malformation, and diaphragmatic hernia (1,2).

The demonstration of the systemic blood supply to the mass definitely facilitates the diagnosis and can guide the future management and possible treatment modalities of this condition.

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Artículos de Revisión:

Farmacoterapia del Dolor Crónico del Paciente Geriátrico

Dr. José C. Román de Jesús*

> El dolor es el límite de nuestra alma.
> Bichat

El paciente geriátrico tiene unas particularidades que no son otra cosa, sino el resultado del proceso de envejecimiento y los cambios degenerativos que le acompañan. Es necesario tomar en consideración la existencia en este tipo de paciente de una gran incidencia de enfermedades concomitantes. Pero, independientemente de éstas, existe un declinar de las funciones orgánicas con cambios de significativa importancia. Podemos enumerar los cambios más evidentes:

1. **Disminución del metabolismo basal** - Se manifiesta por necesitar un menor requerimiento de medicamentos analgésicos, sobretodo, opioides y por observar menor tolerancia a temperaturas bajas. Hay que cuidar, que a veces en nuestros climas la temperatura de las salas de tratamiento se matienen bajas, para contrarrestar el calor, mediante el uso de unidades de aire acondicionado. Nuestros pacientes ancianos la toleran muy mal.

2. **Disminución funcional del sistema nervioso central -** Este es debido a una disminución del flujo sanguíneo cerebral reduciendo los requerimientos de anestésicos locales, opioides y barbitúricos.

3. **Disminuye el reflejo de las vías respiratorias.**

4. **Disminuye la proteína sérica -** Esta reducción deja una cantidad de medicamentos presentes, libres o en estado de gran efectividad. Como resultado, veremos que todo medicamento con aptitud de unirse a las proteínas, debe reducirse. Ejemplo, la bupivacaína.

5. **Aumento del tejido graso -** Esto trae por consecuencias que los opioides liposolubles se almacenen en el tejido graso y de ahí pasen a la circulación y al plasma, lenta y sostenidamente.

6. **Existe disminución de la reserva cardiovascular, del flujo coronario, del índice cardíaco, de la frecuencia cardíaca, de la distensibilidad arterial -** Esta alteración se une al aumento en la resistencia vascular periférica, aumentando a su vez el esfuerzo del ventrículo izquierdo y el débito cardíaco, la presión arterial sistólica y el volumen de choque produciendo una disminución de la respuesta al estrés y a la atropina.

7. **Disminución de la reserva pulmonar -** Se une a la declinación de la capacidad pulmonar total y de la capacidad vital, menor reflejo de tos y tendencia a la depresión respiratoria (sobretodo con opioides).

8. **Disminución de las funciones renales y hepáticas -** Los cambios renales y hepáticos reducen la habilidad del anciano de excretar los medicamentos administrados y la excreción de los desperdicios metabolizados como la creatinina. Como ejemplo de la eliminación de los narcóticos, el fentanil tiene una vida media de eliminación de 265 minutos, en el adulto joven. En el anciano es de 945 minutos.

9. **Disminuye el umbral del dolor en comparación al joven en un 15 - 20% -** Se cree, es debido a la dispersión termal en la piel.

Con estos conceptos en mente analicemos el arsenal farmacológico disponible en el tratamiento del

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dolor crónico en el paciente geriátrico no sin antes considerar que en el dolor crónico entran factores psicológicos, debilitantes de la personalidad, así como de la naturaleza física del que tratamos, con gran impacto familiar.

División y líneas de farmacoterapia:

El dolor crónico se divide en: **menor, leve, moderado y severo,** existiendo siete líneas de farmacoterapia en los últimos tres.

Dolor muscular crónico menor

Este tipo de dolor es menor, pero molesta, sobretodo en el anciano que pasa tiempo inactivo y dirige su atención en su dolor. Los anti–inflamatorios no esteroidales por vía oral son la primera elección. De fallar, a estos pacientes les gustan los medicamentos tópicos. Los medicamentos dentro de esa clasificación actúan como contrairritantes y su acción analgésica se debe a la dilatación vascular, aumentando el flujo sanguíneo al área afectada.
Se consideran los siguientes agentes como efectivos y seguros: el salicilato metílico y el aceite de trementina. Se usa también la capsaicina que parece actúa sobre la substancia P y el capsicum en su foma de oleoresina. Se debe advertir que su suspensión puede causar una irritación excesiva.

Dolor leve

Primera línea de farmacoterapia:

La consideración inicial a ocupar nuestra mente es la utilización de la aspirina. A menos que exista una contraindicación sigue siendo el medicamento de elección. Su dosis de 650 mg. cada 4 horas es la primera línea de farmacoterapia. Es útil en dolores leves y/o moderados como en casos de artritis, dolores de cabeza simples tensionales y lumbalgias.

Se absorbe rápido en el duodeno, no importando tenga buffer o no. Se metaboliza en el hígado y hay que tomar en consideración los cambios mencionados previamente. Se une a la proteína y se insiste en la cautela, cuando se está en anticoagulantes orales, ya que éstos se unen a la proteína en el 97%, por lo que al ingerir aspirinas queda libre una gran cantidad del anticoagulante disponible con las consecuencias de hemorragias masivas. Recordaremos además, su acción farmacológica de inhibir la síntesis de la prostaglandina, siendo, no tan solo antinflamatorio y anlagésico, sino que también es antipirético y altera el agregado plaquetario. Aunque es uno de los agentes mas seguros y efectivos, tiene riesgos: alteraciones gastrointestinales, que varía desde una simple irritación, hasta úlcera y sangrado del tracto digestivo. Se ha asociado con la pérdida de la audición en dosis altas y con leucopenia, plaquetas bajas y anemia hemolítica. La incidencia de personas con sensibilidad alérgica a los salicilatos, es alta, por lo que debemos considerarlo. Otras precauciones: la ingestión oral de hipoglicemiantes, lupus eritematoso sistémico y procedimientos quirúrgicos en perspectiva.

Para los envejecientes que no toleran la aspirina, la alternativa es el acetaminofén. Se usa la misma dosis, teniendo en cuenta que su actividad antinflamatoria es baja. Aunque se sabe su seguridad, se han informado casos de alteraciones hepáticas, aún en dosis bajas. Precauciones: si requiere dosis altas, si existe alcoholismo, si hay compromiso hepático y/o renal y si ha tenido alguna reacción al medicamento.

Segunda línea de farmacoterapia:

De no responder el dolor a los medicamentos señalados hay que considerar una segunda línea de tratamiento. Con esos propósitos están disponibles, principalmente, tres anti-inflamatorios no esteroidales (de ahora en adelante A.I.N.E.S.): ibuprofén, naproxén y ketoprofén. Su acción es semejante a la aspirina. (Fig. 1)

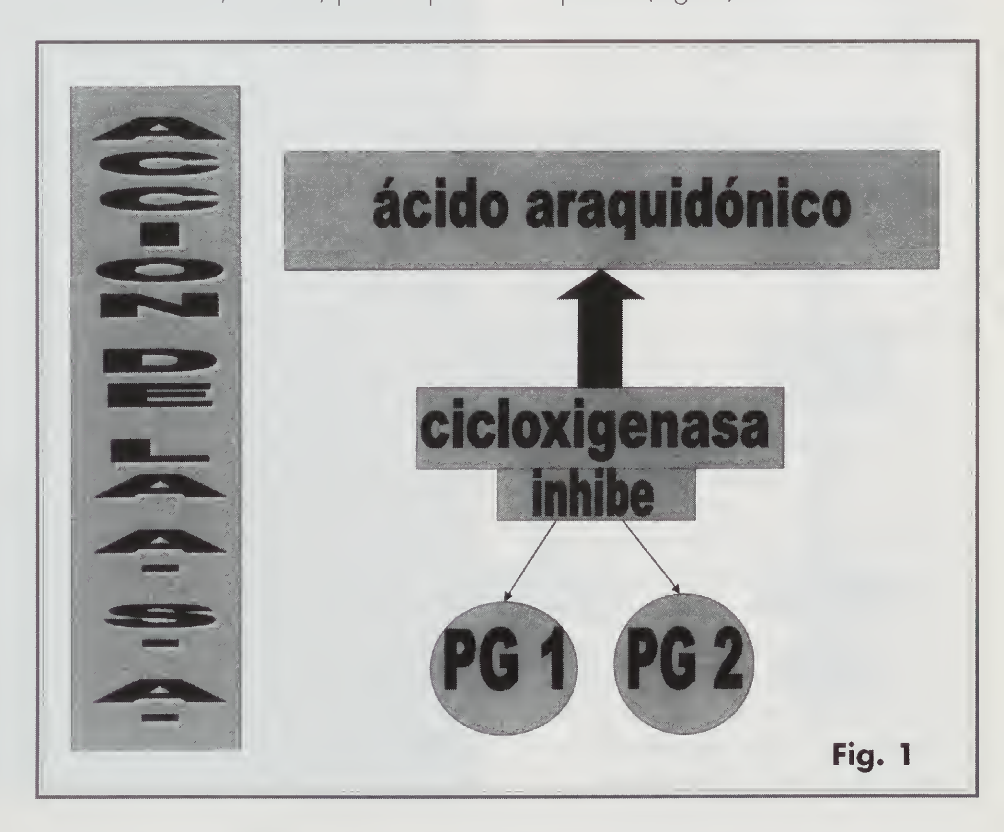


Fig. 1

- **Ibuprofén** - su dosis de 200 mg. 3 - 4 veces al día, tiene, principalmente, efecto analgésico y adhesión anti - plaquetaria. Puede producir efectos adversos severos: dolor gastro - intestinal y/o úlcera. Ha de tomarse conjuntamente con un vaso de agua lleno o con las comidas. **Contraindicaciones:** alergias a aspirina, historia de úlcera péptica, tendencias a hemorragias, disfunción hepática y/o renal, si se ha tomado acetaminofén en forma prolongada y si han existido reacciones adversas a otros medicamentos previamente.

- **Naproxén sódico** - Introducido al mercado en 1974, tiene efecto analgésico, anti-inflamatorio, pero, poca actividad antipirética; poca acción antiplaquetaria. Actúa disminuyendo la concentración de prostaglandinas y se absorbe 100%. Comparándolo con los otros, produce menos efectos gastro - intestinales y menor incidencia de complicaciones hepato - renales. **Contraindicaciones:** asma bronquial, úlceras pépticas, discracias sanguíneas y daño renal. Dosis 220 mg. cada 8 - 12 horas. Se pueda comenzar con doble dosis y no exceder en el anciano 440 mg. en 24 horas.

- **Ketaprofén** - Es ácido fenil - propiónico, de la misma familia que el ibuprofén y el naproxén, con poca actividad anti-inflamatoria. Dosis 12.5 - 25 mg cada 4 - 6hrs. No exceder 75 mg. en 24 horas. Es efectivo en lumbalgias menores, mialgias y dolores artríticos y osteo - artríticos. Por su absorción rápida (se alcanza la máxima concentración entre 30 mins. a dos horas) el efecto máximo es corto aumentando la frecuencia de la dosificación.

Dolor moderado

Tercera línea de farmacoterapia:

De no responder un dolor o alcanza el nivel de moderado, no hay que temer en aumentar la dosis a una tercera línea de terapia. Si un dolor de cabeza no responde a 650 mg. de aspirina, no hay que dudar en subir la dosis a 1,000 mg. Así sucede con los ya mencionados.

Ningún A.I.N.E.S. es más efectivo que otro ni tampoco tiene más o menos toxicidad. Es obvio que al aumentar la dosis, aumenta también los efectos secundarios y las complicaciones.

Cuarta línea de farmacoterapia:

De no responder el dolor al aumento a una tercera línea terapeútica, otro A.I. N.E.S. debe ser tratado. Se recomienda que este segundo agente sea seleccionado de otra familia química.

Complicaciones: Existen menores, como las irritaciones del tracto gastro-intestinal y las severas como la hepatotoxicidad y la nefrotoxicidad. Por tal razón la función de estas nobles vísceras debe monitorizarse de cerca. Aunque dos de estos medicamentos vienen de forma inyectable, no deben utilizarse para dolor moderado.

Los nuevos:

Dos antiflamatorios no esteroidales han salido al mercado: Celecoxib y Rofecoxib. Se alega que en su bloqueo de las prostaglandinas, solo lo realiza ante la acción de la cicloxigenasa 2 (COX 2), dejando libre la cicloxigenasa 1 (COX !) aparentando ésta permitir la producción de prostaglandina 1 (PG !) protectora de la mucosa gastro-intestinal.

Ejemplos:

Familia química	A.I.N.E.S.	Nombre Comercial	Dosis mg.
Acido carboxílico acetilado	Aspirina	Varios	325 - 1,000
Acido carboxílico no - acetilado	Salicilato de colina, magnesio	Trisalate	750 - 1,000
	Diflunisal	Dolobid	250 - 500
	Salsalate	Disalcid	1,000 - 1,500
Acidos acéticos	Ibuprofén	Motrin	200 - 800
	Ketoprofén	Orudis	25 - 75
	Naproxén	Naprosin	250 - 500
	Ketorolac	Toradol	30 - 60
	Oxaprozin	Daypro	1,200 - 1,800
Acidos fenámicos	Meclofenamato	Meclomén	50 - 100
	Ac. Meclofenámico	Ponstel	250
Acidos enólicos	Piroxicam	Feldene	10 - 20
Compuestos no ácidos	Nabumetone	Relafen	500 - 1,000
Acido prirolo - acético	Indometacina	Indocin	25 - 50

Bloqueadores de COX 2	Celecoxib	Celebrex	100 - 200
	Rofecoxib	Viox	12.5 - 25 - 50

Quinta línea de farmacoterapia:

De entender el clínico que un narcótico de acción moderada necesita usarse, éste puede utilizarse en combinación con el A.I.N.E.S. Por ejemplo, si a la aspirina (650 mg) se le une codeína (65 mg) los resultados son excelentes. Un trabajo de Moertel y sus colaboradores demostró que esta combinación es supeior a: oxicodona - aspirina; pentazocina - aspirina; promazina - aspirina, etc. Debe recordarse que al utilizar un opioide, sus efectos secundarios pueden estar presentes.

Sexta línea de farmacoterapia:

Si la combinación codeína - aspirina o parecidas no producen la analgesia deseada, podemos optar por el uso de tramadol. Este agente tiene unas peculiaridades: actúa como un opioide estimulando el opio receptor mu, así como bloqueando la reabsorción de la nor - epinefrina y la serotonina, tal como funcionan los andepresivos mas recientes. No debe utilizarse conjuntamente con un opioide. Su dosis es de 50 a 100 mg. cada 4 - 6 horas, no excediendo 400 mg. en el día. Puede usarse por vía endovenosa, subcutánea o intramuscular en dosis de 100 mg. Es efectivo en paciente con dolor que combina síndromes nociceptivos y neuropáricos, con la dificultad que tarda en tener su efecto máximo, por lo que hay que esperar 10 días para su reevaluación. Existe buena experiencia, en el unir este medicamento al ketorolac por vía endovenosa.

Dolor severo:

Séptima línea de farmacoterapia:

Existen tres criterios que orientan al clínico a decidirse por el uso de un opiode, como agente farmacológico mas potente:

1. Si se ha tratado con medicamentos no opioides previamente en dosis adecuada y por el debido tiempo

2. Si este dolor es mas debilitante que un dolor moderado

3. Si el paciente tiene historial de ser efectivo su control de dolor previo con opioides.

De ser así y cumpliendo con estos tres criterios, podemos entonces usar opioides. La elección principal: morfina. Puede usarse por vía oral, pero nunca debe dudarse que de necesitarse, este excelente opioide debe indicarse por otras vía parenterales. Como agonista puro, ocupa el receptor mu. Los agonistas - antagonistas, aunque tienen un efecto analgésico, obtienen a su vez, un tope, al activar el opioreceptor kappa, bloqueando a su vez el componente de mu, de tal forma que un aumento en la dosis, no aumenta la analgesia (tampoco la depresión respiratoria). Hemos visto que estos medicamentos, en los ancianos, producen disforia, posiblemente por su actuación sobre el opioreceptor kappa.

La dosis de la morfina: oral, de 10 a 100 mg. Por otras vías, ha de usarse lo que siempre señalo: "la que necesite el paciente". Si va a usar un opioide, úselo sin miedo.

Toxicidad: usándolo en dolor crónico, no se ha descrito toxicidad alguna (Kreek, 1973 y 1978). Si existe depresión respiratoria por su efecto en el opioreceptor mu. Pero, volvemos a insistir que en dolor severo, no tiene mayores consecuencias (Mueller, 1982; Martin, 1967; Walsh, 1981; Lipman, 1988). El propio dolor estimula la respiración y existe siempre el temor a la adicción. Un estudio de Porter y sus colaboradores demostró que usando

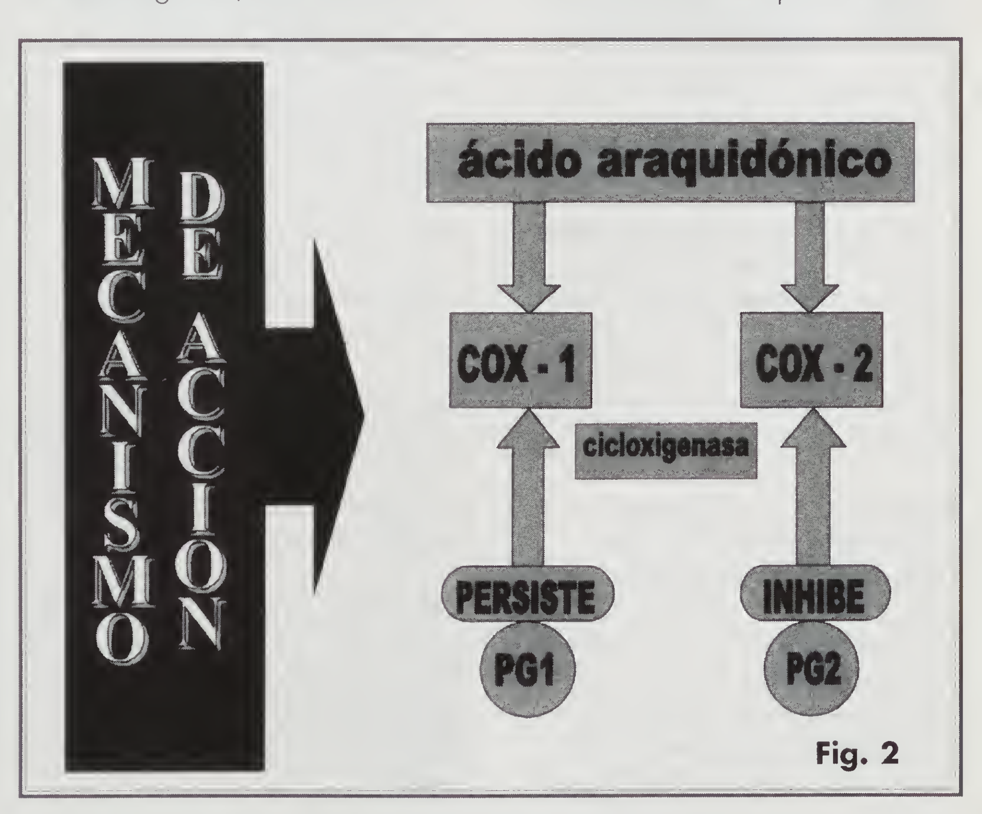


Fig. 2

opioides en 12 mil pacientes con dolor crónico, solo cuatro se convirtieron en adictos (0.03%). En cuanto a la tolerancia o taquifilaxia, se sabe que en dolor crónico, a medida que su uso va a la par al progreso de la enfermedad, se requiere, mayor dosis cada día. Las vías, los métodos, las alternativas son temas de otra charla.

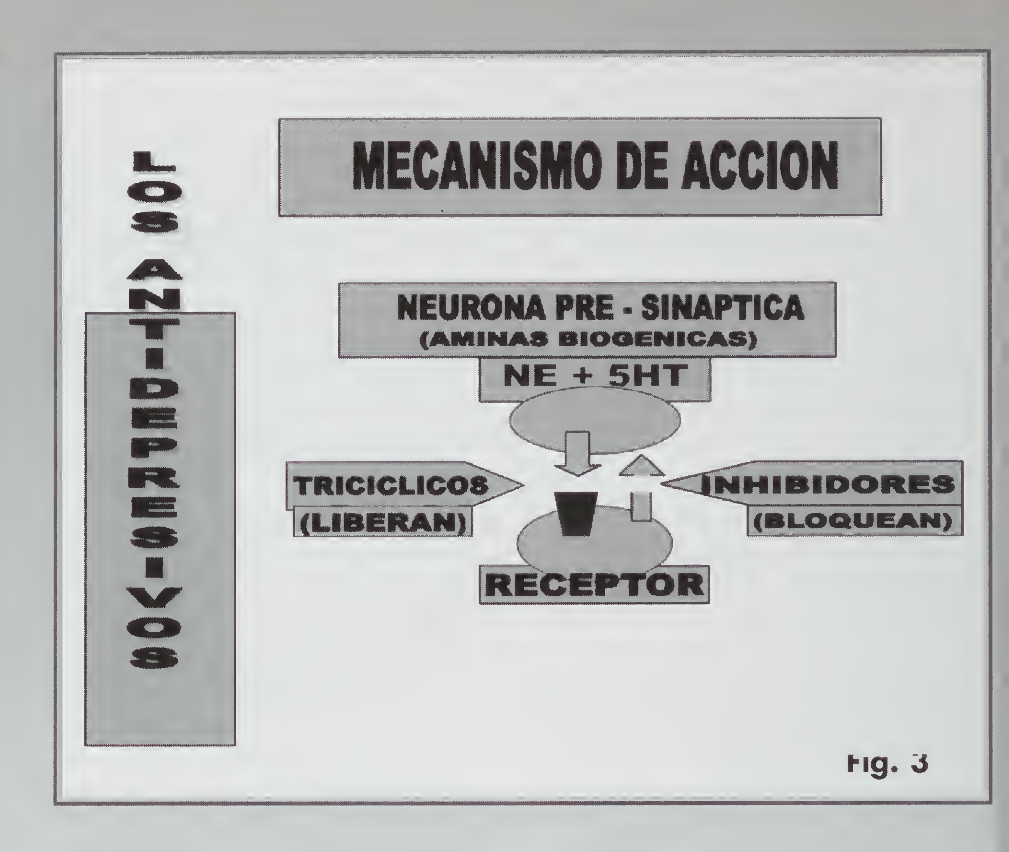


Fig. 3

Otros medicamentos que deben y pueden usarse: Los antidepresivos:

Los pacientes con dolor crónico, mas en el envejeciente, vienen a nuestro servicio con algún grado de depresión. Todavía no está claro, si el paciente se deprime por la cronicidad del dolor, o si por el contrario, al exisistir concomitantemente un cuadro depresivo, hay mayor percepción del dolor. En este tipo de pacientes se unen: la limitación de recursos, el aislamiento y la soledad; la limitación de los medios cognitivos y del entendimiento, la intensificación del sufrimiento y la incomodidad asociada al dolor. De ahí la necesidad de unir a nuestras modalidades terapeúticas, un antidepresivo. Los mas usados: (Fig. 3)

● Tricíclidos: - Estimulan la secreción, principalmente de serotoninas y son efectivos en el dolor crónico. El problema es la presentación de efectos secundarios significativos, sobretodo, en el anciano. Hemos usado el HCl de doxepina en dosis de 25 mg. una o dos veces al día con buenos resultados, aún en el paciente geriátrico.

● Paroxetina: - No obstante, cuando salió al mercado este medicamento, que impide la reabsorción de la serotonina con poco impacto en la nor - epinefrina y en la dopamina, se convirtió en nuestro antidepresivo de elección, en dosis tan bajas, como 10 mg. diarios en el paciente envejeciente.

Los anticonvulsivos:

En el paciente geriátrico, por su edad surgen una serie de condiciones y enfermedades propias de esta etapa de la vida. Es frecuente encontrar síndromes neuropáticos. Estos responden bien a la terapia con anticonvulsivos, unidos a antidepresivos y a bloqueos terapeúticos. Un ejemplo son las neuropatías metabólicas de las extremidades inferiores que responde bien a estos dos medicamentos junto a bloqueos simpáticos lumbares para - vertebrales. Los medicamentos usados son:

● La hidantoína:- Sigue siendo muy útil, de bajo costo, efectiva en dosis inicial de 200 mg, incrementando a un total de 800 mg, con controles de determinación en sangre.

● La carbamazepina:- Se usa igual que el anterior y con la misma dosis. Funciona bien, junto a antidepresivos y a bloqueos neurales en las neuralgias del trigémino.

● La gabapentina:- Nuestras experiencia y estudios recientes (Rosner, Rubin & Kestenbaum, 1996) demuestran la respuesta en 48 horas a la medicación con una reducción significativa del dolor. En algunos casos presenta efectos secundarios, como mareo, vertigo y somnolencia. El control de la dosis puede evitarlos o mejorarlos.

El dolor maligno:

La Organización Mundial de la Salud (OMS) ha determinado que en el dolor crónico de tipo maligno se ha de seguir la norma de los tres escalones o pasos. Estos corresponden a la severidad del dolor: ligero, moderado y severo.

■ Paso # 1 (Ligero) - Se usa aspirina, acetaminofen u otro A.I.N.E.S. conjuntamente con medicamentos coadyuvantes: antidepresivos, anticonvulsivos, antihistamínicos, hipnóticos, cafeína, esteroides, etc.

■ Paso # 2 (Moderado) - Se usa el A.I.N.E.S. unidos a un opioide

mediano, en su potencia por vía oral, con los coadyuvantes.

■ Paso # 3 (Severo) - Aquí es cuando se une a los medicamentos señalados, un opioide potente como la morfina, en la dosis necesaria. Ultimamente se ha estado usando con buenos resultados el parcho de fentanil de 25, 50, 75 y 100 mcg. con duración de la analgesia hasta de 72 horas. Un problema importante es su costo.

Terminaremos hablando del dolor insensible a los opioides. MacQuay, en 1989, lo definió, como aquel que "no responde a la analgesia mediante opioides". Su existencia se da y se explica cuando hay destrucción de nervios, como en accidentes, en tumores, en neuralgias postherpéticas y del trigémino. Es tema de otro escrito.

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Carta:

Quincuagésimo Aniversario de SER

10 de septiembre del 2000

Enhorabuena y saludos, compañeras y compañeros, amigas y amigos.

Me parece increíble, hasta asombroso, hallarme hoy en Puerto Rico pronunciando estas palabras ante este auditorio de amigos bondadosos de la Sociedad de Educación y Rehabilitación. Mucho le agradezco al comité organizador de esta noble Sociedad que hayan invitado a un viejo americano y a su familia a compartir su quicuagésimo aniversario. En este momento, ante ustedes, me sobrecogen muchos sentimientos cuando recuerdo la fundación de la Sociedad y los primeros años de mi profesión de médico fisiatra en Puerto Rico. Tengo muy presente la enorme influencia que tuvo la Sociedad en el nacimiento y crecimiento en Puerto Rico de mi especialidad, la Medicina Física y Rehabilitación, gracias a su ejemplar cuidado médico de discapacitados y minusválidos. Ustedes son, sin duda alguna, verdadero ejemplo vivo del gran postulado moral del equipo de rehabilitación: "No basta sumarle años a la vida, es necesario añadirle vida a los años." Su centro de rehabilitación es una de las razones importantes del reconocimiento mundial que ha recibido Puerto Rico por tener uno de los programas de rehabilitación médica más sobresalientes de cualquier país.

Antes de retrotraerlos cincuenta años, hasta la fundación de nuestra Sociedad de Educación y Rehabilitación, permítanme recordar el nombre del Licenciado Guillermo Atiles Moreu, que en paz descanse. Fue un creyente sincero en el cuido de minusválidos y discapacitados. Mientras fue administrador del Fondo del Seguro del Estado, creó los medios para establecer en Puerto Rico el tratamiento médico definitivo del obrero lesionado, programa que fue líder a nivel mundial y todavía sigue al frente de tales programas. Hombre de un convencimiento trascendental en el cuido de minusválidos y discapacitados de todas las edades, hace cincuenta años Don Guillermo Atiles Moreu fue la chispa, el promotor de la creación de esta Sociedad para el cuido de los niños discapacitados de Puerto Rico. No cabe duda de que el esfuerzo pionero del Licenciado Guillermo Atiles Moreu fue instrumental en promover la aceptación de la Medicina Física y Rehabilitación en todo Puerto Rico. Fue un hombre sabio que contribuyó a la formación de mi carrera médica. Este centro es un vivo monumento al Licenciado Guillermo Atiles Moreu; y, mientras pase un niño por sus puertas, no será olvidado.

Permítanme transportarlos al mes de marzo de mil novecientos cincuenta (parece que fue ayer), cuando el Departamento del Trabajo de los Estados Unidos invitó al Fondo del Seguro del Estado a un semimario en Washington, D.C. para discutir sus experiencias en la rehabilitación de obreros lesionados. El Licenciado Atiles, el señor René Jiménez Malaret, oficial de relaciones públicas, y yo descansábamos en nuestra suite del hotel cuando recibimos una llamada del señor Larry Link, quien se presentó como el Director Ejecutivo de la Sociedad Nacional de Niños y Adultos Lisiados, hoy conocida como la Sociedad para la Venta de Sellos de Pascua Florida. Le interesaba discutir la posibilidad de organizar el capítulo Puertorriqueño de esta Sociedad. Así es como nosotros tres, el Licenciado Atiles, el señor René Jiménez Malaret, y yo llegamos a ser fundadores del capítulo Puertorriqueño, que hoy se llama Sociedad de Educación y Rehabilitación (S.E.R.) de Puerto Rico.

La campaña inicial para recoger fondos se llevó a cabo desde Chicago, enviando por correo Sellos de Pascua Florida a las direcciones de las familias que aparecían en la guía telefónica de Puerto Rico que René se había traído consigo a los Estados Unidos. Puede que les interese saber que la respuesta inicial produjo alrededor de diez mil dólares ($10,000.00), lo que sorprendió a todos. El capítulo de Puerto Rico se organizó en una casa en el Condado y la señorita Judy Constable, una Terapista Ocupacional, fue su primer administrador. Luego se construyó en Hato Rey un impresionante edificio para un centro de rehabilitación y una escuela especial, en terrenos donados por el Fondo del Seguro del Estado y con fondos

provistos por el pueblo de Puerto Rico y, especialmente, donaciones grandes del Honorable Luis A. Ferré y el Sr. Rafael Carrión, Jr., que en paz descanse. La señora Isabel Atiles fue la directora de este centro.

El trabajo de la Sociedad ha sido prodigioso, y Puerto Rico ha sido bendecido por su presencia. Recuerdo con gran aprecio las oportunidades de entrenamiento disponibles a mis residentes cuando el Dr. Carlos Armstrong (que en paz descanse) fue su director médico, y recuerdo con mucho orgullo los incontables cientos de niños y adolescentes discapacitados que han sido educados y tratados en sus programas. Pronto se convirtió en el centro de rehabilitación modelo para el tratamiento de niños minusválidos en el Caribe y en Latinoamérica.

Recuerdo con orgullo haberle referido al centro médicos, terapistas, trabajadores sociales, y otros miembros del equipo de rehabilitación en calidad de aprendices, provenientes de países caribeños y latinoamericanos, enviados por el Departamento de Estado de los Estados Unidos al Servicio de Medicina Física y Rehabilitación de la Administración de Veteranos en Puerto Rico. Sabía, estaba seguro de que se les daría la mejor atención y el adiestramiento más sobresaliente durante su periodo de observación y participación en los programas de rehabilitación del centro. Ustedes hicieron un trabajo estupendo, y sus adiestramientos han beneficiado a cientos de niños discapacitados del Caribe y Latinoamérica.

Con el transcurso de los años, cincuenta exactamente, muchos de los miembros originales del equipo han pasado a mejor vida. Sin embargo, hoy siento sus presencias entre nosotros, y creo que estarían contentos con su progreso de S.E.R. y satisfechos con el éxito de su programa. Con entusiasmo y fervor, ustedes le han provisto nuevas metas a miríadas de niños excepcionales que han tenido la suerte de asistir a su escuela y a sus programas de rehabilitación médica. Ustedes le han dado a los padres de estos niños entendimiento y nuevas esperanzas. Ustedes han transformado a estos jóvenes pacientes en ciudadanos hábiles y productivos, por lo que todo Puerto Rico le estará eternamente agradecido. Saludo al equipo por su trabajo estimulante y su paciencia. Saludo, además, a los estudiantes y a los pacientes por su motivación, porque sin motivación no puede haber progreso. Verdaderamente son ustedes héroes anónimos en este mundo. Dios los bendiga y favorezca siempre.

CELEBRANDO SU CENTENARIO
1902-2002

ACTIVIDADES PROGRAMADAS

CONFERENCIA DE PRENSA CENTENARIO

Fecha: jueves 19 de septiembre
Hora: 11:00 a.m.
Lugar: Asociación Médica de Puerto Rico

ACTO ECUMÉNICO CON MOTIVO DEL CENTENARIO

Fecha: viernes 20 de septiembre
Hora: 7:00 p.m.
Lugar: Asociación Médica de Puerto Rico

CASA ABIERTA

Fecha: 21 y 22 de septiembre (sábado y domingo)
Hora: sábado 9:00 a.m. - 5:00 p.m.
domingo 10:00 a.m. - 2:00 p.m.
Lugar: Asociación Médica de Puerto Rico

VISITA A LA TUMBA DEL DR. MANUEL QUEVEDO BÁEZ

Fecha: sábado 21 de septiembre
Hora: 9:00 a.m.
Lugar: Puerto Rico Memorial, Isla Verde

ORQUESTA SINFÓNICA NOCHE RUSA*

Fecha: viernes 27 de septiembre
Hora: 7:00 p.m.
Lugar: Centro de Bellas Artes de San Juan

*Boletos al venta en la boletería del Centro de Bellas Artes

GALERÍA VIOTA EXHIBICIÓN PINTURAS DE JORGE FELLÍN

Fecha: jueves 3 de octubre
Hora: 7:00 p.m.
Lugar: Galería Viota, Avenida San Patricio

CENA-GALA DEL CENTENARIO

Fecha: viernes 4 de octubre
Hora: 7:00 p.m.
Lugar: Hotel Caribe Hilton, San Juan

VI FERIA INTERNACIONAL DEL LIBRO DE PUERTO RICO

Fecha: sábado 26 de octubre al domingo 3 de noviembre
Lugar: Coliseo Mario "Quijote" Morales de Guaynabo

Este año la VI Edición de la Feria Internacional del Libro de Puerto Rico se le dedica a la Asociación Médica de Puerto Rico en homenaje a la celebración de su centenario.

Todas estas actividades están sujetas a cambios



See package insert for full Prescribing Information.

INDICATIONS AND USAGE

Maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

Short-term treatment (up to 8 weeks) of erosive esophagitis associated with GERD. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor devel opment in humans is unknown

Information for Patients

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0 5 to 200 mg/kg/day, about 0 1 to 40 times the exposure on a body surface area basis, of a 50-kg person dosed at 40 mg/day In the gastric fundus, treatment at 0 5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day In the liver, treatment at 0 5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Oawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors Oose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of combined hepatocel lular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver ONA covalent binding assay Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled ONA synthesis (UOS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother

Pediatric Use

Safety and effectiveness in pediatric patients have not been established

Use in Women

Erosive esophagitis healing rates in the 221 women treated with PROTONIX (pantoprazole sodium) Delayed-Release Tablets in U.S. clinical trials were similar to those found in men In the 122 women treated long term with PROTONIX 40 mg or 20 mg, healing was maintained at a rate similar to that in men The incidence rates of adverse events were also similar for men and women.

Use in Elderly

In short-term U S. clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with PROTONIX were similar to those found in patients under the age of 65 The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

ADVERSE REACTIDNS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two U S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies of GERO patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Orug Related in Short-term Oomestic Trials

	% Incidence			
	Study 300-US		Study 301-US	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term double-blind or open-label clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
Study Event	Pantoprazole Total (N= 2805)	Ranitidine 300 mg (N= 594)	Dmeprazole 20 mg (N= 474)	Famotidine 40 mg (N= 239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more of GERO patients on long-term therapy.

Most Frequent Adverse Events Reported as Drug Related in Long-term Domestic Trials

	% Incidence		
Study Event	PROTDNIX (n = 536)		Ranitidine (n = 185)
Headache	5	2	
Abdominal pain	3	1	
Liver function tests abnormal	2	<	1
Nausea	2	2	
Vomiting	2	2	

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in <1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE. abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction, photosensitivity reaction

CARDIOVASCULAR SYSTEM. abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

OIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC ANO LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM. arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM. asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis extema, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Ouincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis; and rhabdomyolysis In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In two U.S. controlled, short-term trials, 0.4 % of the patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PRDTONIX 20 mg experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed One patient tolerated a dose of 320 mg per day for 3 months. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

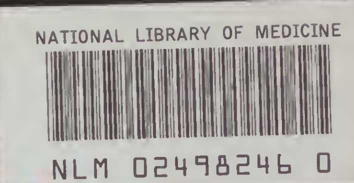
Pantoprazole is not removed by hemodialysis.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

Wyeth

Manufactured for Wyeth Pharmaceuticals
Philadelphia, PA 19101
under license from
Altana Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on the approved PROTONIX Delayed-Release Tablets direction circular (CI 7482-1, Issued June 18, 2001).



Nighttime heartburn: a rude awakening

PROTONIX® tames erosive GERD night after night



PROTONIX is indicated for the treatment and maintenance of healing of erosive esophagitis with associated gastroesophageal reflux disease (GERD) symptoms. Controlled studies did not extend beyond 12 months.

The most frequently reported adverse events with PROTONIX Delayed-Release Tablets are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. **Please see brief summary of Prescribing Information on adjacent page.**

